Journal of Forensic Medicine

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Sponsored by the South African Medico-Legal Society

Editor: H. A. Shapiro, Ph.D., M.B., Ch.B., F.R.S.S.Af.

First South African Medico-Legal Congress

The South African Medico-Legal Society has arranged for this Congress to be held in Johannesburg, from Thursday night, 31 July to Saturday (midday), 2 August 1958. The exact venue of the meeting will be announced later.

The following topics are provisionally scheduled for discussion:

1. *Artificial Insemination.*
2. *A Symposium on Acute Alcoholism.*
3. *Problems of Blood Transfusion.*
4. *A Symposium on Sudden Death in Infancy.*
5. *Problems of Consent to Medical Procedures.*
6. *Two Recent American Films* (in sound) entitled *The Medical Witness* and *The Doctor Defendant* will be screened, followed by a discussion on the films, and an *Open Forum* on any topic discussed at the Congress.

These films have been sponsored by the Wm. S. Merrell Company of Cincinnati, in co-operation with the American Medical Association and the American Bar Association. They have been made specially available for this Congress by the Wm. S. Merrell Company.

7. *Medico-legal Exhibits and a Visit to the South African Blood Transfusion Centre.*

The Congress registration fee for members of the South African Medico-Legal Society is 10s. 0d. The registration fee for non-members is £1 10s. 0d. (The normal subscription for membership of the South African Medico-Legal Society is £2 2s. 0d. This includes a free subscription to the *Journal of Forensic Medicine.*)

Colleagues who wish to register for attendance at this Congress must advise the Honorary Organizing Secretary not later than 30 June 1958. This will enable adequate accommodation arrangements to be made for the meetings and ensure sufficient time for the printing of a Congress prospectus which, it is hoped, will include the names and addresses of all participants in the Congress.

All communications must be directed to:

Honorary Organizing Secretary (Dr. H. A. Shapiro), First South African Medico-Legal Congress, P.O. Box 1010, Johannesburg.

A Percentage Method for Representing the Fall in Body Temperature after Death

Its Use in Estimating the Time of Death

F. S. Fiddes, M.D.*

With a Statement of the Theoretical Basis of the Percentage Method

T. D. Patten, B.Sc., Ph.D.†

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For purposes of estimating the time that has elapsed since death, the importance of noting the body temperature has long been emphasized. Unfortunately, there are so many factors which influence the rate of body cooling that it is a difficult matter to interpret the significance of a single temperature reading, whether this has been taken in the axilla, rectum or elsewhere in the body. In practice, the temperature is considered along with all other circumstances, and a reasonable degree of accuracy may often be achieved. This is by no means possible in every case, however, and if a single temperature reading is the main or sole guide, deductions will frequently be very wide of the mark.

The subject has lately received some critical attention. It has been suggested by Shapiro[1] that some forensic pathologists are prone to invest with unwarranted certainty calculations based on popular rules of thumb, which in his view should be relegated to the realm of medico-legal mythology. His strictures are probably too sweeping, but he has usefully drawn attention to the initial plateau of sustained temperature which characterizes the cooling curve as it applies to the centre of a body, and to the heat conductivity of the body as a factor affecting the rate of cooling. Cooling at the centre of a body is delayed until, by conduction, a temperature gradient is established from the centre to the periphery.

In Ceylon, De Saram[2] has studied the rate of cooling in a series of cases and has endeavoured to express the influence of certain modifying factors by means of a mathematical formula rather than by a general assessment. *Inter alia*, he emphasizes that, in addition to radiation, conduction and convection, evaporation is a further process which plays a significant part in determining the rate of heat loss.

In this country, Sydney Smith and others have stressed the desirability of temperature readings at intervals so that, as well as the extent of the fall at any single point of time being known, the *rate* of fall may be assessed,

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and serve as an indication of how the various modifying factors are in fact operating in a particular case.

There have been recent suggestions that a special type of mechanical or electrical instrument is essential for the recording of temperatures in the dead body. Such instruments are undoubtedly convenient and of real value for certain purposes, but the use of a standard chemical thermometer is by no means outmoded. Insistence on the need for special apparatus might well defeat the object in view, for it may not be available. Certainly it is unlikely to be at the disposal of a practitioner called to the scene of a murder, and often enough he is the first person able to take the necessary readings.

Experimental Observations

Despite the evidence of great variability, the cooling rate of the body would seem to be of such potential value as an index of the time since death that anything which makes for greater accuracy of interpretation is of considerable practical importance. The present article is the outcome of an experimental study of cooling rates with the object of devising, if possible, an improved method of interpretation having at least some measure of general application. In all, over 100 bodies have been observed experimentally and the results analysed in a variety of ways.

These observations have extended over the past 4 years, suitable cases being selected as and when they presented. It was essential that the time of death should be known precisely and that, so far as could be judged, there was no reason for supposing that the deceased's temperature was other than 'normal' at the time of death. It was desirable that little time should have elapsed between death and arrival at the mortuary, and there should have been little disturbance of the body or its coverings in the interval.

The selected cases included both males and females, varying considerably in build and stature, and in the amount of clothing present on the body. These factors were noted in each case, and in the more recent cases the actual weight was taken. The bodies were placed in the same part of the mortuary, on the same wooden-topped trolley, covered with a thin sheet. The observations were made under varying seasonal conditions, the prevailing atmospheric temperatures ranging from 40°F. to 70°F.

In the early stages of the investigation, the rectal temperature was recorded at intervals by means of a standard chemical thermometer, the atmospheric temperature being noted at the same time. Soon, however, the method was adopted of recording the rectal and atmospheric temperatures by means of an electrical continuous recording apparatus.* As has already been suggested, such a method is much more convenient and suitable for experi-

* (Cambridge 2-point Electrical Temperature Recorder.)

mental purposes, but is in no way essential for obtaining isolated readings, either single or at intervals, as would often be required in practice.

For the most part, selection was restricted to those cases in which custody of the body was likely to be retained for a length of time sufficient to permit of complete cooling, but short-term records have also been used to check the validity of the conclusions drawn from the more complete records. Records have also been obtained in a number of cases in which abnormal conditions were present, e.g. known pyrexia at death, marked variation in environmental temperature, etc. and these have been retained for future reference and further investigation.

Average Rate of Cooling

The observations gave early confirmation of considerable variation in the rate at which dead bodies cool. Table I records the figures obtained from a series of 20 cases, male and female, varying in size and amount of clothing, and in various environmental temperatures, the highest being 58°F. and the lowest 46°F.

Table I

Hours After Death	*Fall in Rectal Temperature (Presumed 99·0°F. at Death)*		
	Minimum	*Maximum*	*Average*
0—4	4·0°	9·5°	7·6° i.e. average of 1·9° per hour
0—6	7·0°	12·5°	10·2° i.e. average of 1·7° per hour
0—8	9·0°	15·0°	12·7° i.e. average of 1·6° per hour
0—10	11·0°	18·0°	15·3° i.e. average of 1·5° per hour
0—12	13·0°	20·5°	17·5° i.e. average of 1·46° per hour
0—15	17·0°	24·5°	21·1° i.e. average of 1·4° per hour
0—18	20·0°	27·5°	24·0° i.e. average of 1·3° per hour
0—21	23·0°	30·5°	26·7° i.e. average of 1·27° per hour
0—24	26·0°	33·0°	29·1° i.e. average of 1·21° per hour
0—30	30·0°	37·0°	33·0° i.e. average of 1·1° per hour
0—36	33·0°	41·0°	36·0° i.e. average of 1·0° per hour

The averages for the first 12 hours conform closely to the simple formula which has been suggested for that early period, viz.:

$$\frac{98{\cdot}4^\circ - \text{Rectal Temperature}}{1{\cdot}5} = \text{Approximate Number of Hours since Death.}$$

For subsequent periods the averages show no very significant disagreement with other general estimates which have been made. It is obvious, however, that the range of temperatures observed at the different time intervals precludes any rule of thumb application of general formulae. The figures simply confirm the need for caution and the possibility of error, especially in the earlier hours after death, if reliance is placed on a single temperature recording.

Virtual Temperature Difference and Virtual Cooling Time

It also became clear, not only that bodies varied considerably in the cooling rate and therefore in the time taken to cool, but that in the conditions described, which were by no means extraordinary, the cooling time was on the average much longer than is commonly stated. It was not unusual to find that 60, 70, or more hours were required before atmospheric temperature was reached.

As the atmospheric temperature is approached, the rate of cooling becomes very slow indeed, and a substantial part of the complete cooling time is occupied by the last few degrees of temperature drop. This was inconvenient in that it so greatly prolonged the recording time for each body. More important, it was obvious that when the temperature of the body had fallen to within 7°F. or thereby of the atmospheric temperature, the recording of that temperature could be of no value in assessing the time of death with any degree of accuracy. It was decided, therefore, to disregard the last 15% of the difference between normal body temperature and the prevailing atmospheric temperature, and to consider that the body was virtually cooled when its temperature had fallen through the first 85% of that difference. Thus arose the concept of 'Virtual Cooling Time' and 'Virtual Difference in Temperature at Time of Death' which were used subsequently in place of the actual difference in temperature and the time required for complete cooling.

Although the figure of 85% was decided upon empirically from a study of the cases thus far observed, it was later confirmed that this figure is also acceptable from a theoretical point of view. As the body temperature was recorded in the rectum, the normal temperature at the time of death was assumed to be 99·0°F. rather than 98·4°F.

Percentage Cooling Rate

The new concepts could not alter the fact that bodies cooled at different rates. One body might be 'virtually' cooled in 30 hours; the next might require more nearly twice that length of time. But the first would also be half-cooled in a shorter time than the second. The question was: Would that time be correspondingly and proportionately shorter? To find the answer, the temperature recordings were interpreted, not in hours and degrees, but in percentages of the virtual cooling time and of the virtual temperature difference. As the number of suitable cases accumulated, it became apparent that there was, in fact, a close correspondence, and Table II shows the average percentage figures from 50 cases studied in this way. They were 'selected' only in the sense that they did not include cases where the circumstances were known or suspected to be 'abnormal', e.g. pyrexial illness before death, protracted death, marked variation in environmental

circumstances after death, etc. They varied from flimsily-clad, slightly-built young females and frail old men, to stout well-covered males and plump fur-coated women. The prevailing atmospheric temperatures ranged from 40°F. to 70°F.; the virtual cooling times from 30 hours to 70 hours.

Table II: Percentage Cooling Rate

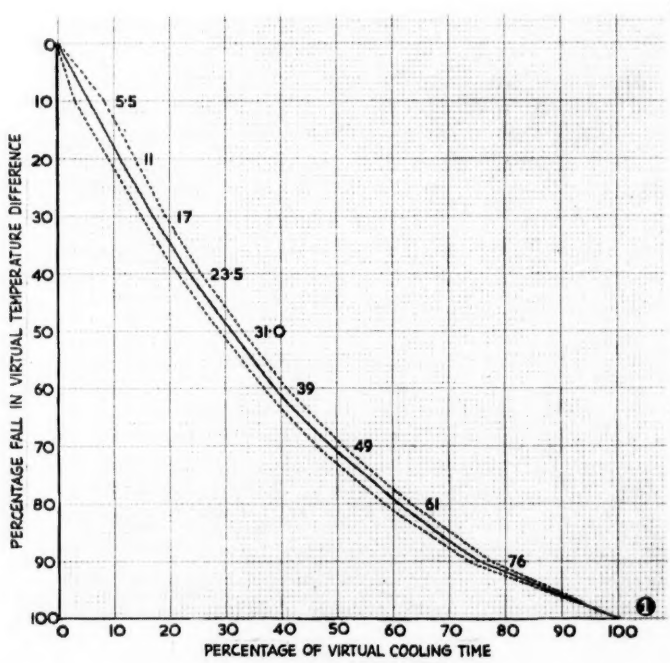
Fall in Rectal Temperature (Presumed 99°F. at Death)

Amounting to	10	20	30	40	50	60	70	80	90	100	per cent of V.T.D.
Occurs in	5·5	11	17	23·5	31	39	49	61	76	100	per cent of V.C.T.

V.T.D. = Virtual temperature difference at the time of death (i.e. 85% of the total difference between rectal and atmospheric temperatures).

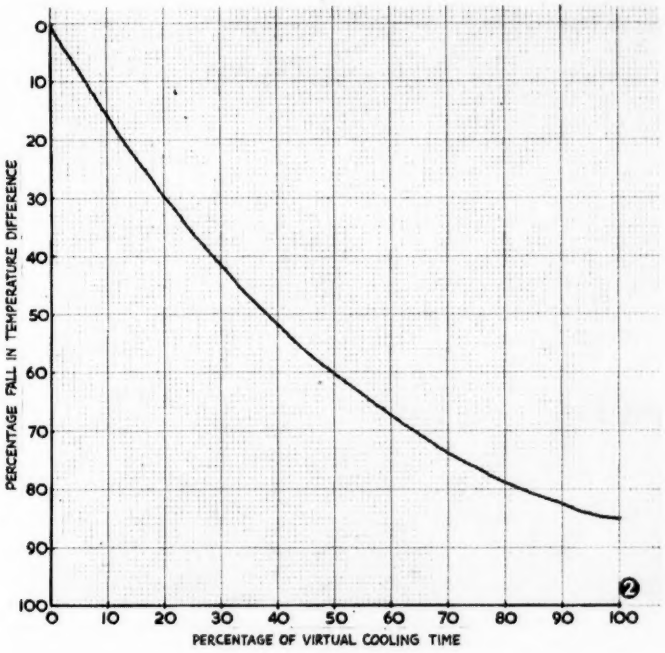
V.C.T. = Virtual cooling time (i.e. the time required for the rectal temperature to fall through the virtual temperature difference).

Fig. 1 shows the same average figures in graph form, and also indicates the limits within which the calculated percentages fell.



It is, in fact, unnecessary to make use of the 'virtual' temperature difference at all, so long as it is appreciated that this provides the basis for reckoning the virtual cooling time, which is an essential factor in the calculations.

Fig. 2 shows the same average figures as above, again in graph form, but with the temperature factor expressed in terms of the total difference between the presumed rectal temperature at the time of death and the prevailing atmospheric temperature.



As previously stated, experimental observations were also made in a number of cases in which the recording could only be continued for a relatively short time. In these cases, sections of the partial record of temperature fall were used in conjunction with a graph such as is shown in Figs. 1 or 2. The purpose was to check still further the validity of the percentages shown on the graph, and the results were satisfactory in that they showed a close degree of conformity.

In these 'control' cases, of course, the actual time of death was known, but the method of using the graph (Fig. 2) would be the same in unknown cases and when the temperature can only be recorded at intervals. The method can be illustrated by considering a hypothetical case, for example:

The body of a man is found dead in a house at 11.30 *a.m.*
Rectal temperature is determined first at 12 noon and again at 3 p.m.
Presumed rectal temperature at death = 99°F.

Prevailing atmospheric temperature in the room (say) = 52°F.
Therefore the temperature difference at the time of death = 47·0°F.
Rectal temperature at 12 noon (say) = 83°F.
i.e. a drop of 16°F. = 34% of the temperature difference.
Rectal temperature at 3 p.m. (say) = 79°F.
i.e. a drop of 20°F. = 42·6% of the temperature difference.

By reference to the graph in Fig. 2, it is seen that:

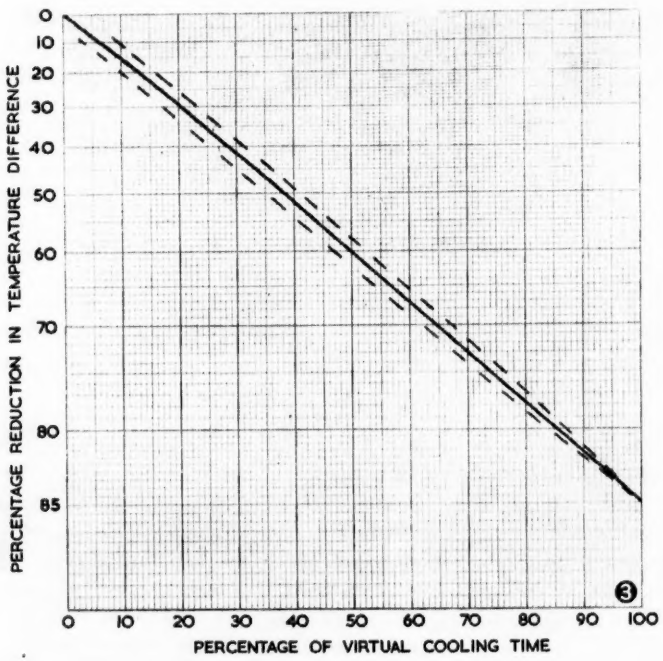
A fall through the first 34% of the temperature difference occupies 23·5% of the virtual cooling time.

A fall through the first 42·6% of the temperature difference occupies 31·0% of the virtual cooling time.

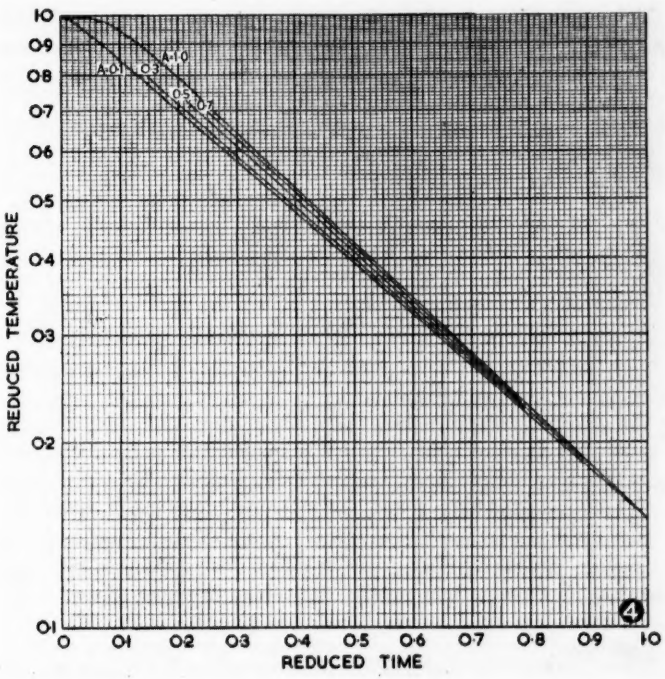
Therefore in this case, 7·5% of the virtual cooling time = 3 hours (12 noon to 3 p.m.).
Therefore the virtual cooling time = 40 hours.

At noon, 23·5% of the virtual cooling time had already elapsed, i.e. 9·4 hours.
Therefore the time of death was approximately 2.30 a.m.

When the percentage cooling rates are projected on logarithmic graph paper, the result is a line which is straight, except in the first or top part of its extent where a slight flattening no doubt reflects the initial plateau of sustained central temperature referred to by Shapiro.[1] The line is shown in Fig. 3, which also indicates the limits of variation.



This form of graph is perhaps even better adapted for reference than either of the curved lines previously given. It is of greater significance to learn that the calculated rate of cooling at the centre of a solid cylinder, similarly expressed, follows a very similar line, as is seen in Fig. 4.



Indeed, the average line in Fig. 3 corresponds almost exactly with the line for the lowest calculated value shown in Fig. 4. Alterations in the diameter and thermal properties of the cylinder cause variation in the position of the line similar to the variations given by different cooling human bodies. The theoretical calculations are considered later, but the point of immediate interest is the close general similarity shown between the behaviour of the dead body and that of the theoretical cylinder when their cooling rates are investigated and expressed by the proposed percentage method.

Discussion

From the results of the experiments described, it would appear that, although bodies vary greatly in actual cooling rate and therefore in time taken to cool completely, there is in fact a close *proportional* correspondence in their cool-

ing rates which remains undisturbed by difference in sex, size, coverings and atmospheric temperature.

To demonstrate this correspondence, it is necessary to make use of the virtual temperature difference and the virtual cooling time, as defined above. They are determined by disregarding the lowest 15% of the actual temperature difference, through which the fall is prolonged and erratic, being influenced by even minor alteration in the environmental circumstances. The correspondence appears when the percentage cooling rates are estimated on this basis.

There is a close similarity between the experimental results and those given theoretically by a cooling solid cylinder, when regarded in the same way. It would appear that a dead body, in cooling, behaves like any other mass of matter of corresponding bulk, and that the variations found are determined by variations in the size and thermal properties of individual bodies. This similarity should probably be regarded as strong support for the validity of the experimental results. It has long been felt that the dead body must conform with the same laws as other inanimate matter, but the similarity has been difficult to demonstrate because of the variable factors influencing the rate of cooling.

In the examination of the dead body, the percentage cooling rate curve can be used in estimating the time that has elapsed since death. If two or more temperature readings are taken over the space of several hours and the prevailing atmospheric temperature is noted, reference to the curve will permit the estimation of the virtual cooling time and thence the time since death to within an hour or so on either side of the average. It may be possible to say on which side of the average line the answer is likely to lie. Further investigations at present in progress are designed to explore this possibility.

In making estimates by this method, it is essential that the body should remain undisturbed. Movement of the body from place to place, and marked change in the environmental circumstances will invalidate any conclusion drawn. In this connexion, it is relevant to note that the experimental cases were in fact subject to the movement necessary for removal to the mortuary. It may well be that the rate of cooling in the early stages after death was rather more rapid than would be found in bodies left absolutely undisturbed, and that further observations will show that the line of the percentage cooling rate requires slight modification. A related problem which is also under consideration is the practicability of calculations which will render the method applicable even when there have been distinct phases of marked environmental change, either by movement or otherwise.

Body temperature in these experiments was recorded in the rectum. In preparing the percentage cooling rates, the rectal temperature at death was presumed to be 99·0°F. This is probably the best figure to use, but if the

rectal temperatures were considerably higher (or lower) at death, deductions would be correspondingly misleading. There is something to be said for the use of liver temperature rather than rectal temperature. In many cases it might involve less disturbance of the body for recording purposes. The validity of applying the cooling rates shown above by the fall in liver temperature after death would require confirmation.

Summary

The fall in body temperature after death can be represented by the percentage method described which automatically makes allowance for the differences in the thermal properties inherent in different bodies and their coverings, and is unaffected by the level of the atmospheric temperature, provided that this remains relatively constant.

Further investigation is called for in a number of directions, and the suggested cooling rates may require slight modification in the light of further experience; nevertheless it is considered that these rates are fairly accurate if the circumstances are reasonably 'normal'.

The method is capable of being applied in estimating the time that has elapsed since death in cases where the body has remained undisturbed and there have been no violent fluctuations in atmospheric temperature.

The application of the method is essentially practicable in that it requires only the recording of the rectal temperature on 2 or more occasions over the space of several hours, during which the body must remain otherwise undisturbed. The significance of these recordings is then interpreted by means of the percentage cooling rate graph.

Grateful acknowledgement is due to Sir Sydney Smith, under whose auspices the experimental observations were commenced; also to Dr. W. D. L. Fernando, now in Ceylon, for his valuable assistance in the early stages of the investigation.

I am much indebted to Prof. Douglas Kerr, who has co-operated throughout and, by his sustained interest and practical participation, has greatly facilitated the experimental work and contributed to the results achieved.

An important part has been played by Dr. T. D. Patten, Lecturer in the Department of Engineering, Edinburgh University, who has been closely associated with the investigation and whose co-operation has been invaluable in interpreting the significance of the results obtained in terms of the many thermal considerations involved. Dr. Patten's statement of the theoretical basis of the percentage method, although presented for convenience in the manner of an Appendix, represents an essential part of the investigation.

At this point, it is perhaps appropriate to add that I should be grateful for information on any instances in which it proves practicable to take temperature readings at intervals in the manner suggested, with a note about the circumstances. Such information would assist greatly in assessing the practical value of the percentage method.

Appendix

The Theoretical Basis of the Percentage Method for Representing the Fall in Body Temperature after Death

If the problem posed is to predict theoretically the variation with time of

body temperature after death, this is only possible if a simplified form can be considered.

The simplest model is a solid cylinder of homogeneous material. This is assumed to lose heat through the cylindrical surface only and not at the ends, i.e. an infinite cylinder.

The problem is now a 2-dimensional heat transfer problem.

Before a solution can be found some assumptions must be made. These are:

1. The cylinder of radius 's' is initially at a uniform temperature throughout, equal to V.

ii. The cylinder is of homogeneous material with the following constant physical properties, thermal conductivity 'k', density 'p', and specific heat 'c'.

iii. This cylinder at uniform temperature V, with no internal source of heat, is placed in an atmosphere of uniform temperature U so that initially the heat loss rate will depend on the temperature difference (V–U) and a constant surface heat transfer coefficient per unit area 'h'. The heat loss rate at the surface depends at all times on the difference between the surface temperature and the environment, and only initially is this (V–U). (This quantity h may be considered to take into account heat transfer by convection, radiation and evaporation at normal temperature differences.)

At any time t after the surface begins to cool, the temperature difference between any point in the body at radius r and the atmosphere is $(V_{rt}-U)$ and the 'percentage fall in temperature difference' is

$$\frac{V - V_{rt}}{V - U} = 1 - \frac{V_{rt} - U}{V - U}.$$

It is convenient at this stage to define 'the reduced temperature' corresponding to V_{rt}, i.e. 'v_{rt}' as $\dfrac{V_{rt} - U}{V - U}$. In this way the initial and final reduced temperatures of the cylinder are always 1 and 0 respectively.

The expression for the solution is simplified if the following groups are used:

$$a = k/\rho c \tag{1}$$

$$\Lambda = sh/k \tag{2}$$

The reduced temperature v_r of any point at radius r ($0 \ll r \ll s$) in an infinite solid cylinder at any time t is (Carslaw and Jaeger)

$$v_r = \sum_{n=1,2\ldots}^{\infty} e^{-\beta n^2 a t/s^2} \cdot \frac{2\Lambda J_o(r\beta_n/s)}{(\beta_n^2 + \Lambda^2)J_o(\beta_n)} \tag{3}$$

$J_o(x)$ is the Bessel function of order zero of the first kind.

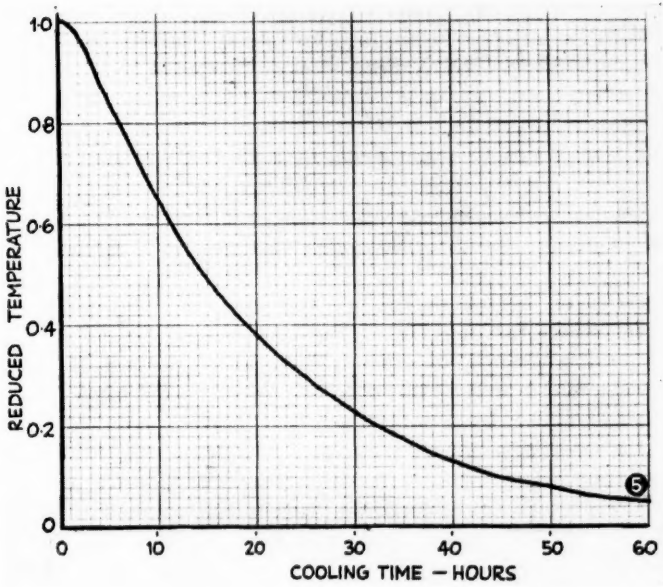
$\pm\beta_n$, $n = 1, 2, 3, \ldots$, are the roots of

$$\beta\, J_1(\beta) = \Lambda J_o(\beta) \tag{4}$$

Assuming that in the case of bodies, the temperature measured is that at the axis of the cylinder, $r = 0$, then at any time t,

$$v_o = \sum_{n=1,2\ldots}^{\infty} e^{-\beta_n^2 a t\, s^2} \cdot \frac{2\Lambda}{(\beta_n^2 + \Lambda^2)J_o(\beta_n)} \tag{5}$$

For any one case, by the assumptions made, A is constant. Therefore β_n and $J_0(\beta_n)$ are fixed and v_0 depends only on t.



The variation of v_0 with t is as shown in Fig. 5. The time taken to reach $v_0 = 0$ is infinity and in order to discard the final portion of the cooling curve v_0 is plotted against τ, the reduced time, which is the same as the percentage of the 'virtual cooling time'. The reduced time is defined as the period of time required for v_0 to reach a value of 0·15. This value was chosen after consideration of the accuracy of experimental measurement.

The general expression for v_0 in terms of τ is

$$v_0 = \sum_{n=1,2\ldots}^{\infty} e^{-\sigma \cdot \frac{\beta_n^2}{\beta_1^2} \tau} \cdot \frac{2\Lambda}{(\beta_n^2 + \Lambda^2) J_0(\beta_n)} \qquad (6)$$

where $\sigma = \dfrac{\log. \overline{(0{\cdot}15(\beta_1^2 + \Lambda^2) J_0(\beta_1)}}{\log. e}$ (7)

Equation (6) is now independant of a and therefore differences in ρ and c will not affect any theoretical relationship of this form.

Thus two immediate advantages of this expression are the removal of:

1. The long 'tail' of the curve as the body approaches atmospheric temperature.
ii. The effect of a on the time scale.

If this relationship is now plotted on logarithmic graph paper, a further advantage is realized as shown in Fig. 4 for values of A from 0·1 to 1·0, viz. the later stages of cooling are characterized by straight lines. This occurs because the magnitude of the terms due to n = 2, 3 . . . ., etc., is negligible after 15 to 20% of the reduced time. Beyond this time, v_0 is given accurately by the expression,

$$v_0 = e^{-\sigma\tau} \frac{2A}{(\beta_1^2 + A^2)J_0(\beta_1)} \qquad (8)$$

which is an exponential curve giving a straight line on logarithmic graph paper.

Fig. 4 includes the complete curves for A = 0·1 and 1·0 calculated from equation (6) and curves for other different values of A calculated from equation (7).

These curves are now the basis for comparison with experimental temperature records such as in Fig. 3. The difference in scales used in the two figures will be noted. These scales are only nominal; conversion of reduced temperature to percentage reduction in temperature difference is gained by multiplying (1 — reduced temperature) by 100.

The advantage claimed for this approach to the problem via Fig. 4, is that with further experience it should be possible to allow for, and finally, to predict, variations in A, due to any variation in h, s or k. Possible variations may be considered to arise from some of the factors shown in Table III.

Table III: Factors Influencing Variation in Cooling Rate

Surface Heat Transfer Coefficient, **h**	*Representative Diameter of Body*, **2s**	*Thermal Conductivity of Body Matter*, **k**
Atmospheric Conditions: Wind; Humidity	Mean diameter of body	Internal variations with size: Density, plumpness, etc., characterized by a Length / Diameter ratio
Surface Conditions: Clothing Covering; Degree of exposure		Variations associated with sex

Because of the similarity of the experiments of De Saram carried out during the same period, it might be of value to compare the two theoretical methods.

The approximate equation quoted by De Saram and equation (8) of this paper are of the same form. Equation (8) has only been included here because it simplifies the drawing of the curves when $\tau > 0{\cdot}15$ or 0·2. In his context De Saram has stipulated that there is an initial temperature lag with an average value of 45 minutes. The complete curves of Fig. 4 have,

however, incorporated in them the value of initial temperature lag which depends in theory on the value of A.

The fundamental difference, therefore, is that we do not accept an average value of this 'initial temperature lag' but hope to be able to fix its value implicitly in individual cases by a knowledge of the particular conditions which occur. It is hoped that the removal of this restriction will result in greater accuracy at small values of the reduced time, and in the end allow the production of a series of practical values of A (to be used in conjunction with Fig. 4) which apply universally.

References

1. Shapiro, H. A. (1954): J. Forensic Med., **1,** 158.
2. De Saram, G. S. W. *et al.* (1955): J. Crim. Law. Criminol., **46,** 562.

Burns and Freezing

As a Cause of Peptic Ulceration*

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Acute peptic ulceration following cutaneous burns is well known although rarely seen. Most textbooks of surgery, pathology and forensic medicine mention the subject, usually under the heading of *Curling's ulcer.* The observation had, however, been made already in 1823 by Swan[34] and suggested by Dupuytren[10] in 1832. Other early cases were described by McFarlane,[26] Cooper[4] and by Long[25]; but Curling[5] was the first to give a detailed survey of the subject, based upon 10 cases, 4 of which were personal observations. In 1866 Curling added a fifth case.[6] All these were instances of *acute duodenal ulcers* with fatal complications and the term *Curling's ulcer* ought to be limited to such cases.

Several case reports and a few surveys have appeared during the last century. Harkins[15] reviewed 107 cases, of which 94 died and were submitted to autopsy. In 1942 he reviewed 10 further cases.[16] The survey was completed by Weigel *et al.*,[35] who reported 5 and reviewed a further 17 cases from the preceding decade. Other excellent surveys were given by Pack,[29] Keeley[24] and Friesen.[12] By now the number of reported cases exceeds 150.

Statements concerning *the frequency* of gastro-duodenal ulcerations following burns have varied widely. The frequency can best be estimated in fatal cases submitted to autopsy. However, several experienced pathologists have never seen a case and a few even regard the whole matter as a myth. Others have reported incidences of 25% or even 36% in small series. Friesen[12] reported 38% and Hartman[18] even 63% in experiments on dogs. In Harkins' review the average incidence estimated from 680 necropsied cases of fatal burns was 3.8%.

An appreciable number of the reported cases occurred in children. The mean age in Curling's original series was 11 years, and in Harkins' review

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it was 14.6 years. However, cases occurring in patients 68 and 70 years of age are also recorded. Unlike ordinary ulcers, those occurring after burns are most frequent in females. In Harkins' review they amounted to 72%.

In the great majority of cases the ulcers were duodenal, but some were gastric and a few were reported in the small intestines. Only a very few cases of oesophageal ulceration or perforation are on record.[9, 11, 20, 30-32] A further case with perforating oesophagomalacia is reported below.

Most duodenal ulcers were solitary but in some cases two 'kissing ulcers' or even three, were present. Gastric ulcers were sometimes juxta-pyloric, but more often multiple and superficial. Sometimes both the stomach and the duodenum were involved, and a single case displayed ulceration in oesophagus, stomach and duodenum.[2]

The ulcers were usually demonstrated from a few days to a few weeks after the burn. The average interval between burning and death has been stated as 11-15.4 days, with outer limits of 18 hours and a few months. In most necropsied cases death was due to ulcer complications, either haemorrhage, perforation or both.

Nearly all reported cases concern acute ulcers. In a very few cases, burns have been followed by chronic peptic ulcers, radiologically demonstrated or confirmed at autopsy months or even years after the burn. In one case[28] a gastric carcinoma probably originated in an ulcer scar following a burn.

Acute gastroduodenal ulceration following death from the exposure to cold is a very rare occurrence. Förster[13] reported the case of a 20-year-old inebriated man with frostbite of both legs who died from peritonitis. The autopsy disclosed 5-6 acute duodenal erosions and ulcers, one of which had perforated. Another case was reported by Adams[1] in a 36-year-old man who died 3 weeks after frostbite of the legs. Multiple duodenal ulcers were found in this case.

A case with multiple gastric erosions following freezing is reported below (Case 6). So far as the author knows, no similar case is on record.

A large number of theories has been advanced about *the pathogenesis* of acute ulcers occurring after burns. Only a few of the most important original ones will be briefly mentioned. Dupuytren noticed intense congestion of the brain and gastro-intestinal mucosa in fatal burns. Curling observed congestion, especially of the duodenum, and thought that the duodenal glands had to compensate for the skin, leading to inflammation and ulceration. Hunter[22] observed ulcerative duodenitis following excretion of certain poisons in the bile in dogs. Several subsequent authors have attributed the ulcers following burns to the excretion of various toxins (histamine and others) through the duodenal glands or the bile.

Brown-Sequard[3] assumed a spinal reflex from the burned skin to the ulcerated viscus and later authors have advanced similar theories.

Several cases have been attributed to thrombo-embolic processes, although it seems difficult to explain why these should especially manifest themselves in the duodenum. This could, however, be due to a concomitant gastric hypersecretion. Septic emboli originating in the burned and inflamed skin have also been blamed.

Most recent authors ascribe the ulceration to some of the effects of shock. Both Hartman[18] and Friesen,[12] from experimental evidence, concluded that the most important single factor was haemoconcentration. Others have stressed an adrenal factor. Weiskotten[36] found adrenal necroses and haemorrhages in most fatal burns, and some reported cases of ulceration following burns actually displayed evidence of adrenal lesions. The theory of the adrenal factor is supported by McLaughlin,[27] who produced gastrointestinal ulcers in dogs by electrocauterization of the adrenals. This affords a close parallel to the well known fact that acute severe stress (the adaptation syndrome of Selye[33]) may lead to gastroduodenal ulceration. Cortisone or ACTH may likewise induce acute ulcers in otherwise healthy stomachs or promote perforation of previously existing chronic ulcers. This will be further discussed in a succeeding paper.

Report of Six Cases

This paper is part of a more extensive investigation concerning oesophago-gastro-duodenal ulceration encountered at autopsy. The basic material of 4,317 hospital and medico-legal autopsies has been mentioned in previous papers.[7, 8] Among 208 cases encountered with acute ulceration (including the malacias) 3 had occurred after burns and one followed freezing. Of the 117 cases with chronic peptic ulcer, one appeared due to a burn.

Three cases (Nos. 3, 4 and 5) originated from The Institute of Forensic Medicine, Copenhagen, Denmark, and 2 (Nos. 1 and 6) from The Gade Institute, University of Bergen, Norway. One further case (No. 2), a typical Curling's ulcer, previously observed at The Gade Institute, is included.

The total number of fatal burns submitted to autopsy at the 2 Institutes during the time covered by the investigation was 18, but 5 of these were so severely burned that no detailed study of the stomach was possible. Excluding these, 31% of the fatal burns displayed ulceration.

In all, 4 deaths were ascribed to freezing.

Case 1 (J. 226). A 7-year-old boy was admitted in severe shock following a third degree burn (80% of the surface) from boiling water. The shock was successfully treated and later on skin was grafted. The condition appeared satisfactory during the first few days. On the 12th day,

however, vomiting, dyspnoea and melaena supervened. Death ensued on the 13th day.

Post-mortem examination 7 hours after death revealed an emaciated body; weight 17 kg. Pus was present beneath the extensive skin crusts. The brain was oedematous and the liver appeared pale.

The oesophagus was normal. Numerous punctate haemorrhages were present in the gastric mucosa. *In the superior part of the duodenum 3 ulcers were found.* One, on the posterior wall, was 10 × 5 mm.; the others, on the posterior wall and minor curvature, were 2-3 mm. Only inconspicuous infiltration was noted. The intestinal contents were dark.

Histological examination of the duodenal ulcers revealed well marked borders with scanty granulation tissue containing lymphocytes and a few fibroblasts, but no real fibrosis (Figs. 1 and 2).

Case 2 (J. 387). A 2-year-old boy, rescued from a burning house, had sustained 2nd and 3rd degree burns of the face and both hands and forearms, totalling approximately 20% of the surface. The burns were cleaned with iodine spirit and covered with cod liver ointment; 170 ml. serum were given intravenously. During the next 2 days the condition was fairly good. On the third day, however, the temperature was 38.6°C., a sudden collapse occurred and death ensued before a transfusion could be given. No mention of haematemesis or melaena was made.

Post-mortem examination 36 hours after death revealed yellow-brown, parchment-like skin corresponding to the burns. The organs were markedly pale, notably the liver and the kidneys.

The oesophagus was normal. The stomach and intestines contained plenty of blood. *Just below the pylorus, an acute duodenal ulcer was found.* Its diameter was 2 cm. and the margins were sharp but not infiltrated. An eroded artery was clearly visible. A second acute ulcer, which was pea-sized and shallow, was present 3 cm. below the pylorus on the anterior duodenal wall. Death was ascribed to the extensive gastrointestinal haemorrhage.

Case 3 (J. 321). A 21-year-old man sustained a burn (from flaming benzene) involving 60% of the surface. The burn was mostly third degree. Blood transfusions and Dextran were given and the burns covered with Lucosil ointment. During the following days the temperature rose to 41.3°C. and the patient was semicomatose. Penicillin, blood transfusions and fluids were given. On the 8th day respiratory failure and oedema were obvious. The condition deteriorated, collapse and cyanosis occurred and death ensued on the 12th day.

Post-mortem examination 45 hours after death showed that nutrition had been somewhat subnormal. Extensive crusts, scales and areas of parchment-like skin were seen, corresponding to the burns. The right arm was slightly oedematous. The renal cortex was pale and the marrow hyperaemic. Histo-

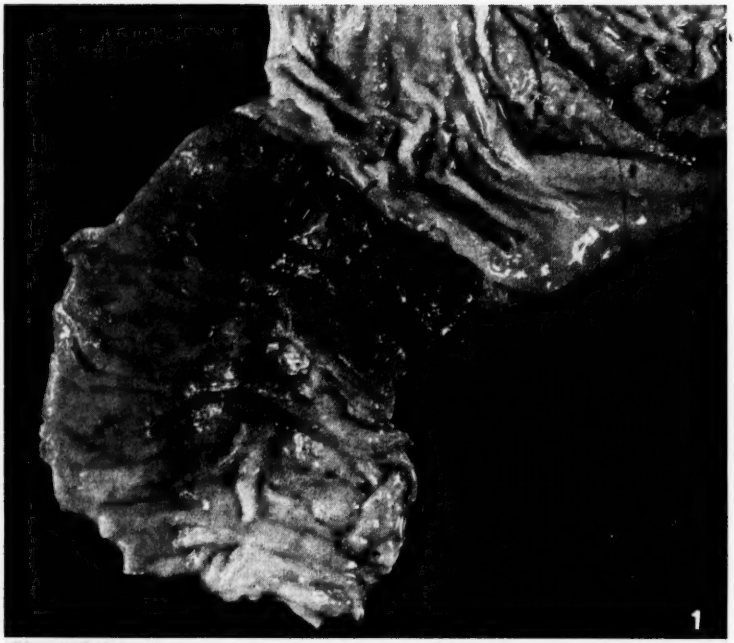

Fig. 1. (*Case 1*). Three acute duodenal ulcers (Curling's ulcers) in a 7-year-old boy died 13 days after a severe burn. Death was due to haemorrhage from an eroded artery (double arrows).
Fig. 2. Photomicrograph of one of the minor ulcers seen in Fig. 2. Note the absence of fibrosis and major inflammatory reaction.

logical examination of the kidneys disclosed a marked hyperaemia at the cortico-medullary boundary, but the tubular epithelium was too autolysed to permit further conclusions. No casts were seen. The suprarenal cortex displayed degeneration.

The pleural cavities contained 400 and 200 ml. haemorrhagic fluid and the peritoneal cavity contained a 100 ml. greenish acid fluid, all originating from *extensive perforations of the lower part of the oesophagus and of the gastric fundus.* No localized ulcers were found.

Case 4 (J. 316). A 3-year-old boy succumbed in a burning house. The autopsy, performed about 12 hours *post mortem,* revealed burns, mostly third degree, of 80% of the surface. The mucosa of the air passages was covered by particles of coal dust, and the blood and all the organs were wine red, indicating coal gas poisoning. Epidural pseudohaematomata were present. Several organs, including the liver and spleen, and even some of the intestines, were somewhat dry from the effect of heat. The brain and meninges were hyperaemic.

The oesophagus was intact. *The gastric fundus displayed a large perforating gastromalacia* with extrusion of 300 ml. of acid gastric contents and remnants of food into the abdominal cavity, beneath the left diaphragmatic dome. No localized ulcers were found and the duodenum appeared normal.

Case 5 (J. 329). A 24-year-old previously healthy man sustained a severe burn from flaming oil and was admitted to hospital semicomatose and in shock. Second and third degree burns involved both legs, part of the face and the major part of the back, totalling about 60% of the surface. Blood, Dextran and serum were given. The burns were treated with silver nitrate ointment and penicillin was administered. Later on skin was grafted.

The general condition remained poor and the course was complicated by a tendency to contractures, bed sores, pyarthron of both knee joints, gangrene of the right foot and a urethral fistula. He remained subfebrile and displayed respiratory difficulties with obstruction by mucus.

Operative extensions of the contractures were performed. Abscesses developed in the bed sores, requiring incisions. The condition was constantly poor, he deteriorated and eventually died in an extremely emaciated state 6 months after the accident.

It should be noted that on the 18th day he had complained of epigastric pain of some days' duration, especially during the intake of milk. Four months after the accident, black vomiting occurred and he became very ill with a feeble pulse. Three weeks later a similar course of events was reported.

Autopsy was performed 41 hours *post mortem.* The body (Fig. 3) proved extremely emaciated (weight 32 kg., height 165 cm.). Hardly any musculature or subcutaneous fat was present. In several places, notably on the back and lower extremities, bones protruded through extensive necrotic sores. The right foot was gangrenous.

Internal examination revealed somewhat atrophic organs (heart: 215 g.; liver: 1,360 g., pale; spleen: 195 g., pale and flaccid). Basal bronchopneumonias were present and pus was found in the bronchi. The kidneys appeared normal but the bladder was inflamed and contained a few very small stones.

Histological examination of the liver revealed a moderate fatty degeneration. The structure of the kidneys was normal, apart from tubular degeneration, which might have been *post mortem*. No amyloid was found in liver, spleen or kidneys. Sections from the lungs revealed massive pneumonia. Sections from the adrenals were not taken.

Fig. 3. (*Case 5*). Appearance of a 24-year-old man at death, 6 months after a severe burn from flaming oil. Extreme emaciation and numerous large necrotic sores with protruding bones are seen.

Fig. 4. (*Case 6*). A 52-year-old man was frozen to death. Numerous haemorrhagic erosions are visible in the gastric mucosa. The gastric contents were haemorrhagic.

The oesophagus was normal. The gastric fundus was adherent to the diaphragm. *A large ulcer, 3 cm. in diameter and at least 2 cm. deep, was present high on the major curvature.* The ulcer penetrated through the diaphragm on the left side and passed into the base of the left lung, which was adherent. The duodenum and intestines were normal without ulceration or haemorrhage.

Histological examination of the ulcer revealed a superficial necrosis and a chronic non-specific inflammatory infiltration with lymphocytes and pronounced fibrosis (chronic peptic ulcer).

Case 6 (J. 373). A 52-year-old healthy man disappeared while skiing in the mountains and was found dead 2 days afterwards. He had sustained injury to one femur and appeared to have sat down and ultimately frozen to death. Autopsy revealed a haematoma in the right quadriceps but no fracture or other major injury. The rest of the autopsy was essentially negative, apart from a slight cerebral oedema and the presence of *about* 20 *haemorrhagic erosions, with superficial loss of substance, scattered in the gastric mucosa* (Fig. 4). The gastric contents were markedly haemorrhagic. The oesophagus and duodenum were normal.

Histological examination of the gastric ulcerations revealed haemorrhagic oedema with necrosis and infiltration, with a few polymorphnuclears but neither fibrosis nor chronic inflammatory reactions. The ulcers were restricted to the mucosa. Sections from the brain revealed only oedema.

Death was ascribed to freezing.

Discussion

Of the 6 cases reported here, the first 2 concerned acute fatal duodenal ulcers occurring in children, 7 and 2 years old, respectively. In both cases death was ascribed to haemorrhage from the ulcers. These cases are in every respect examples of typical Curling's ulcers, identical with those previously described by others.

The other cases are different. In Case 3 both oesophagomalacia perforating into the pleural cavities, and gastromalacia with perforation of the gastric fundus, were present at autopsy. Unfortunately, no histological examination of the perforations or adjacent serous membranes was performed for the demonstration of possible vital reaction. The large amount of fluid in the pleural cavities and notably the contamination with blood appears, however, strongly indicative of vital perforations. The clinical course with sudden collapse and respiratory difficulties is consistent with this view. In this case adrenal cortical degeneration but no adrenal haemorrhage was demonstrated.

The fourth case, with perforating gastromalacia in a boy who died from the combined effects of burns and coal gas intoxication, is questionable but is included for the sake of completeness. It is not known how long the boy survived in the burning house, but apparently it could not have been for long. Histological examination was not performed and it appears most likely that the perforation occurred after death.

However, the malacias always seem to have their cause in the living,[7] a fact which was stressed long ago by Hunter.[21] The author's main material includes 208 cases of acute oesophago-gastro-duodenal ulceration, 125 of

which were instances of oesophago- or gastro-malacia. In the majority of cases acute cerebral lesions were present, in some cases severe intoxication with cerebral involvement was apparent and in the few remaining cases acute severe stress with evidence of shock was obvious.

In the case here concerned no underlying cause could be demonstrated other than the burn and coal gas intoxication. The author is therefore inclined—with some doubt—to ascribe the perforating gastromalacia to these influences, sustained during the last minutes of life.

The fifth case is remarkable. The prolonged case history was dominated by other very severe complications, but included statements about epigastric pain, haematemesis and shock which could easily be ascribed to the ulcer. This was very large and situated at an unusual place high on the major curvature. It had penetrated the diaphragm and even passed into the base of the left lung. Both gross and histological examination revealed convincing evidence of a chronic ulceration.

As the burn was the initial and causal accident in the previously healthy young man, the case should unequivocally be accepted as one of chronic peptic ulcer arising after, and due to, a burn. As appears from the case history and Fig. 3, the case might also be classified as due to prolonged extreme stress.

The last case, with multiple haemorrhagic erosions in the stomach of a man, frozen to death, is even more unusual. Obviously the erosions were quite acute, as blood was found only in the stomach and duodenum, but not below that level. No other cause of death or of gastric irritation was revealed at the medico-legal autopsy. It may be a matter of dispute whether the acute ulceration in this case should be ascribed directly to the exposure to cold or included in the ill defined group of ulcerations due to severe stress.

Only one of the cases reported here (Case 3) revealed evidence of adrenal cortical degeneration, but histological examination was not performed in the remaining cases. Some of the case histories include positive statements of initial shock, which presumably might have existed in all cases. Haemoconcentration, the role of which has been stressed especially in the experimental work,[12, 18] may well have been present. The patients also revealed evidence of cerebral involvement in the acute phase. In the absence of detailed haematological and neurological observations and special histological examinations, however, the author will refrain from a detailed discussion about the possible pathogenesis of the ulcerations in the cases reported here. When viewed in relation to the other cases of acute ulceration encountered by the author, it appears reasonable to assume a cerebral factor or an adreno-cerebral mechanism, even in the cases here concerned, and haemoconcentration may well be involved.

It is appropriate to recall the final statement in the first and usually overlooked paper on the subject, the one-page description of Swan (1823).[34]

He was aware of the inter-relationship between cerebral and gastrointestinal involvement in cases of burns:

'There can be no doubt that the diseased appearance of the head (engorged cerebral membranes, present author's note) and stomach were produced by the irritation of the skin.'

Summary

The author reports 5 necropsied cases of oesophago-gastro-duodenal ulceration following severe cutaneous burns. Two were instances of acute duodenal ulceration (Curling's ulcer) in children who died of haemorrhage from the ulcers. One young man died from perforating gastro- and oesophago-malacia 12 days after a severe burn. Gastromalacia was also present in an infant burned to death.

One young man died in an extremely emaciated state 6 months after a severe burn followed by numerous complications. A large chronic gastric ulcer penetrated into the left lung.

A 52-year-old man who had frozen to death, displayed numerous acute haemorrhagic erosions in the gastric mucosa, and haemorrhagic gastric contents.

The lesions observed in the cases described here are identical with those encountered in other cases of oesophago-gastro-duodenal ulceration, due to cerebral involvement.

References

1. Adams, S. (1863): Amer. Med. Times, **6**, 101.
2. Bothe, F. A. and Magee, R. B. (1953): Pennsylv. Med. J., **56**, 642. Abstr. J. Amer. Med. Assoc., **153**, 1054.
3. Brown-Séquard, E. (1858): Lancet, **2**, 545.
4. Cooper, S. (1839): Lond. Med. Gaz., **23**, 837.
5. Curling, T. B. (1842): Medico-Chir. Trans. Lond., **25**, 260.
6. Curling, T. B. (1866): Lancet, **1**, 484.
7. Dalgaard, J. B. (1957): Acta Pathol. Microbiol. Scandinav., **41**, 1, x.
8. Dalgaard, J. B. (1957): J. Forensic Med., **4**, 110.
9. Davis, J. H. (1953): *Quoted by* Weigel *et al.*
10. Dupuytren, B. A. (1832): *Leçons Orales de Clinique Chirurgicale*, 1832. Read in Bruxelles, ed. 1836.
11. Fisher, cited by Harkins.[15]
12. Friesen, S. R. (1950): Surg., **28**, 123.
13. Förster, A. (1861): Würzburger Med. Zeitschr., **2**, 164.
14. Hansen, G. A. (1945): Ugeskr. f. Læger, **107**, 1101.
15. Harkins, H. N. (1938): Surg., **3**, 608.
16. Harkins, H. N. (1942): *The Treatment of Burns.* Springfield: Charles C. Thomas.
17. Harris, R. I. (1929): Brit. J. Surg., **16**, 677.
18. Hartman, F. W. (1945): Ann. Surg., **121**, 54.
19. Hewett, P. (1847): Trans. Path. Soc. Lond., **1**, 256.
20. Humphrey, G. M. Cited by Harkins.[15]
21. Hunter, J. (1772): Phil. Trans. Lond., **62**, 447.
22. Hunter, W. (1890): Trans. Path. Soc. Lond., **41**, 105.
23. Hunter, W. (1890): Brit. Med. J., **1**, 76.
24. Keeley, J. L. (1929): Amer. J. Surg., **45**, 85.
25. Long, J. (1840): Lond. Med. Gaz., **25**, 743.
26. McFarlane, J. (1833): *Quoted by* Johnson (*Editorial*) in Med. Chir. Rev., **19**, 529.

27. McLaughlin, C. W. (1933): Arch. Surg., **27**, 490.
28. Maes, U. (1930): Ann. Surg., **91**, 527.
29. Pack, G. T. (1926): Arch. Path., **1**, 767.
30. Prosinger, F. (1950): Münschen. Med. Wchnschr., **92**, 279.
31. Rankin, L. M. (1945): Amer. J. Surg., **67**, 134.
32. Robson, L. C. (1943): Brit. Med. J., **1**, 414.
33. Selye, H. (1946): J. Clin. Endocrinol., **6**, 117.
34. Swan, J. (1823): Edin. Med. Surg. J., **19**, 344.
35. Weigel, A. E., Artz, C. P., Reiss, E., Davis, J. H. and Amspacher, W. H. (1953): Surg., **34**, 826.
36. Weiskotten, H. G. (1917): J. Amer. Med. Assoc., **69**, 776.
37. Weiskotten, H. G. (1919): *Ibid.*, **72**, 259.

Fatal Barbiturate Poisoning

A Survey Based on Eighty-Four Cases

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This laboratory has during the past few years made many toxicological analyses in cases of fatal poisoning by barbiturates. A considerable body of data on barbiturate poisoning has thereby been collected, and the writer has examined this in some detail.

This paper overlaps to some extent a recent study by Copeman,[28] but that was not available to the present writer when he started this paper. In any case, this paper goes considerably further than Copeman's into certain aspects of the subject, particularly the differences between the results obtained with different types of barbiturates.

The post-mortem material received comprises usually the brain and the complete viscera (heart, lungs, stomach and contents, liver, intestine and contents, spleen, kidneys), generally with the addition of urine, and sometimes with the addition of blood, vomit, stomach washings, etc. The analytical routine is as follows:

Each organ, and any blood exuded from it, after having been weighed, is minced separately (which ensures that a portion is then a representative sample), an aliquot is dispersed using a top-drive macerator and the barbiturate extracted by the method of Valov.[1] The extract is purified by vacuum sublimation and weighed, and an identification made by X-ray powder analysis of the purified material or of its p-nitrobenzyl derivative.[2] (In the earlier cases listed in Table I the identification was made by 'classical' methods, as the X-ray apparatus was not available at the time they were done). The extract from each organ is weighed separately, and the total absorbed drug present in the body estimated from the average concentration in the solid organs. (It may be noted that this figure is taken as $\frac{\text{Weight of Drug Extracted from Solid Organs}}{\text{Total Weight of Solid Organs}}$, and *not* as the mean of the concentrations in the individual organs).

Table I gives, in a somewhat shortened form, the details of the 84 cases on which this study is based.

Certain organs which are customarily submitted for analysis are omitted from Table I. The alimentary tract is excluded, because the normal routine of analysis does not distinguish between unabsorbed material in the lumen and absorbed material in the tissue of the walls. The kidneys are excluded, because they are commonly lumped with the spleen when submitted; it is unfortunately therefore almost always impossible to make a reliable and independent estimate of the concentration in the kidneys.

Table I: Details of cases

Case No.	Barbiturate	Sex	Age	Time, i.e. Ingestion to Death (Where Known)	Percentage Concentrations in: Liver	Brain	Solid Organs (Average)	Urine
1	Allobarbitone	F	78	4 days	·0006	·0008	·0006	*
2	Barbitone	F	46	4 days		·0044	·0031	
3	Unidentified	F	28	1 day	·0071	·0090	·0085	·0120
4	Pentobarbitone ..	F	49	3 days	·0070		·0070	Ante-mortem ·0100 p.m. ·0025
5	Cyclobarbitone ..	M	31	4 hours ..		·0144	·0120	
6	Butobarbitone	M		3 days ..	·0102	·0098	·0105	
7	Amylobarbitone + Quinalbarbitone	F	66			·0019	·0052	
8	Amylobarbitone + Quinalbarbitone + Cyclobarbitone	F	49	< 8 hours ..		·0047	·0083	
9	Barbitone	M	73	< 8 hours ..		·0160	·0195	·0990
10	Phenobarbitone ..	F	37	< 8 hours ..	·0250	·0130	·0174	·0200
11	Barbitone	F	51			·0210	·0283	
12	Barbitone	F	45	1 day	·0300		·0288	·0820
13	Phenobarbitone + Amylobarbitone	F	52	< 12 hours ..		·0090	·0130	
14	Amylobarbitone ..	F	57	3½ hours ..	·0220	·0100	·0151	
15	Unidentified	M	55		·0015	·0005	·0013	
16	Amylobarbitone ..	M	65			·0141	·0087	·0086
17	Barbitone	F	53	3 days		·0088	·0127	
18	Phenobarbitone ..	F	48			·0140	·0235	
19	Phenobarbitone ..	M	52			·0330	·0515	·0250
20	Pentobarbitone ..	M	70			·0085	·0186	·0382
21	Barbitone	F	37	30 hours ..		·0072	·0065	Ante-mortem ·0630 p.m. ·0370
22	Allobarbitone	F		2 days ..		·0130	·0179	·0047
23	Quinalbarbitone ..	F	34	1 hour (?) ..		·0240	·0204	·1120
24	Mainly Amylobarbitone	M	48			·0032	·0052	·0280
25	Amylobarbitone ..	F				·0094	·0114	·0058
26	Butobarbitone	F	79		·0329	·0079	·0191	·0055
27	Pentobarbitone ..	F	53		·0246	·0030	·0143	
28	Phenobarbitone ..	M	29		·0188	·0093	·0150	
29	Phenobarbitone ..	F	42	2 days ..	·0135	·0082	·0118	·0710
30	Quinalbarbitone ..	M	28		·0155	·0129	·0143	
31	Butobarbitone	M	76	6½ hours ..	·0121	·0055	·0098	·0170
32	Pentobarbitone ..	M	41		·0007	·0074	·0041	·0040
33	Amylobarbitone ..	M	53	< 8 hours ..	·0030	·0015	·0030	
34	Amylobarbitone + Phenobarbitone	F	39	< 8 hours ..			·0036 Ph ·0380 Am	·0550 Ph ·1410 Am

* A blank space indicates that the organ was not available, or not separately available.

Table I: Details of cases (*Continued*)

Case No.	*Barbiturate*	*Sex*	*Age*	*Time, i.e. Ingestion to Death (Where Known)*	*Percentage Concentrations in:*			
					Liver	*Brain*	*Solid Organs (Average)*	*Urine*
35	Barbitone	M	40	22 hours ..	·0112	·0083	·0101	·0233
36	Phenobarbitone ..	M	44	2½ days	·0195	·0167	·0181	Ante-mortem ·0560 p.m. ·0378
37	Barbitone	M		27 hours ..	·0168	·0268	·0206	
38	Quinalbarbitone ..	M	66	30 hours ..		·0045	·0053	·0051
39	Pentobarbitone ..	M	71	< 8 hours ..		·0054	·0331	
40	Phenobarbitone ..	M	46	1½ days ..	·0085	·0107	·0114	·0556
41	Amylobarbitone + other barbiturates	M	47	> 6 hours ..	·0093	·0080	·0079	
42	Phenobarbitone ..	F	59	2½ days ..	·0135	·0154	·0162	·0365
43	Mixed, mainly Amylobarbitone	M	56	2½ days ..	·0183	·0116	·0161	
44	Phenobarbitone ..	F			·0340	·0207	·0240	
45	Amylobarbitone ..	M			·0226	·0082	·0135	
46	Butobarbitone	F	64	< 6 hours ..	·0137	·0051	·0096	·0294
47	Butobarbitone	F			·0198	·0131	·0160	
48	Amylobarbitone + Pentobarbitone	M	75	< 8 hours ..	·0222	·0124	·0182	·0093
49	Amylobarbitone + Quinalbarbitone	M	66	< 8 hours	·0180	·0120	·0136	
50	Amylobarbitone + Quinalbarbitone	F	43	40 hours	·0300	·0323	·0305	·0347
51	Barbitone	F	55	20 hours ..	·0403	·0402	·0397	·1040
52	Quinalbarbitone ..	M		< 8 hours ..	·0023		·0027	
53	Cyclobarbitone ..	M	49	1 day ..	·0281	·0362	·0270	·0947
54	Barbitone	F	68		·0261	·0227	·0207	
55	Amylobarbitone ..	M	64		·0170	·0111	·0160	·0276
56	Amylobarbitone ..	F	66	4 days ..		·0014	·0021	·0100
57	Pentobarbitone ..	F	43	< 7 hours ..	·0027	·0080	·0024	·0037
58	Amylobarbitone + Barbitone ..	M	53	2½ days ..	·0222	·0107	·0114	·0059
59	Quinalbarbitone ..	M			·0075	·0110	·0104	·0082
60	Barbitone	F	80		·0165	·0239	·0215	·0749
61	Barbitone	F	68		·0152	·0115	·0114	
62	Butobarbitone (+ ?) ..	F	45		·0063	·0082	·0065	·0417
63	Butobarbitone	M	62	4 days	·0171	·0069	·0102	·0608
64	Unidentified	M	29	2½ days ..	·0010	·0032	·0021	
65	Pentobarbitone ..	F	63		·0088	·0126	·0097	
66	Amylobarbitone (+ ?)	M	40		·0157	·0100	·0129	·0258
67	Pentobarbitone ..	F	60	>8< 12 hours	·0241	·0063	·0158	
68	Amylobarbitone ..	M	47	< 7 hours ..	·0320	·0125	·0191	
69	Amylobarbitone ..	F	54		·0246	·0134	·0186	·0285

Table I: Details of cases (*Continued*)

Case No.	*Barbiturate*	*Sex*	*Age*	*Time, i.e. Ingestion to Death (Where Known)*	*Percentage Concentrations in:*			
					Liver	*Brain*	*Solid Organs (Average)*	*Urine*
70	Butobarbitone	F	76			·0105	·0120	·0098
71	Amylobarbitone ..	F	31		·0319	·0061	·0158	
72	Barbitone	F	48	5 days	·0138	·0128	·0132	·0145
73	Amylobarbitone ..	M	59		·0128	·0077	·0108	·0172
74	Cyclobarbitone ..	F			·0132	·0071	·0114	·0240
75	Amylobarbitone ..	F	24		·0276	·0065	·0191	·0143
76	Amylobarbitone ..	F	47	2 days	·0147	·0102	·0127	·0293
77	Pentobarbitone ..	F	62	$<$ 6 hours ..	·0273	·0051	·0143	·0138
78	Barbitone (+ ?) ..	F	58	ca. 16 hours ..	·0185		·0194	a.m. ·1290 p.m. ·0590
79	Barbitone (+ ?) ..	M	63	$>$ 3 days ..	·0146	·0094	·0118	a.m. ·0870 p.m. ·0290
80	Quinalbarbitone ..	M	52	5½ hours ..	·0087	·0021	·0067	·0002
81	Barbitone	F	55		·0369	·0300	·0333	·0447
82	Amylobarbitone ..	M	52		·0097	·0033	·0069	
83	Phenobarbitone ..	M	66	$>$ 6 days ..	·0096	·0028	·0072	
84	Pentobarbitone ..	F		2½—3 days ..	·0082	·0040	·0057	·0187

* A blank space indicates that the organ was not available, or not separately available.

The basic data given in Table I may be classified in several ways, and give rise to several obvious questions. Both of these categories may be summarized as follows:

1. The concentration in the tissues at death and, by derivation, the probable amount ingested.
2. The differences between individual barbiturates.
3. The distribution in the body.
4. Sex differences.
5. Age differences.
6. The correlation between the amount ingested and the time of survival.
7. The significance of the amount present in the urine.

1. Concentration in the Tissues

An *a posteriori* inference about the MLD of barbiturates for Man made from this material is bound to be only tentative, since most of the subjects were suicides who, in most cases, took all they could get, which was usually much more than enough.

There does, however, seem to be an upper limit to the amount that can be absorbed before death stops absorption. This appears to be in the neighbourhood of 0.04-0.05%, or even less for the quicker-acting barbiturates. It is quite common, in cases where a large amount is subsequently recovered from the organs, to find numbers of recognizable, scarcely digested capsules in the stomach contents.

In Case No. 19, which shows the highest average concentration in the solid organs of any case examined, 10.06 g. phenobarbitone were recovered from the stomach contents, in addition to the very large amount recovered from the other organs. In another case (No. 71) the average concentration of amylobarbitone in the solid organs was 0.0158%. If we assume a flesh weight for the deceased (a young woman) of 50 kg., this figure corresponds to 7-8 g. absorbed barbiturate in the whole body, yet in this case no less than 27.5 g. were recovered from the stomach and intestines, the bulk of which was certainly present unabsorbed in the lumen of the alimentary tract.

The literature contains little in the way of systematically presented records of the probable dosages in fatal cases. Thrower[29] considers that a blood concentration of 0.015% w/v of barbiturate is 'the maximum which can be tolerated without endangering life'. In making this estimate, however, he draws no distinction between different groups of barbiturates. His figure actually lies between the mean values found here of the concentrations of the long-acting, and all other types. (Tables II, IV and VI.) According to Burger[3] 'approximately 10-15 times the usual hypnotic dose [of any barbiturate] may become toxic'. This statement is discussed in the next section.

2. Individual Barbiturates

The barbiturates actually encountered have been grouped according to the usual classification into:

(*a*) Long-acting [barbitone (Veronal, Embinal); phenobarbitone (Luminal, Gardenal)].

(*b*) Intermediate-acting [allobarbitone (Dial); amylobarbitone (Amytal); butobarbitone (Soneryl)].

(*c*) Short-acting [cyclobarbitone (Phanodorm); pentobarbitone (Nembutal); quinalbarbitone (Seconal)].

Cases in which the barbiturate was not identified, or in which it was a mixture of barbiturates from different groups, are not considered in this section.

(*a*) *Long-Acting Barbiturates.* This group numbers 26 cases, the figures for which are summarized in Table II and Fig. 1.

In a number of previously reported cases of fatal barbitone and phenobarbitone poisoning[4-7] the figures quoted all fall within the limits shown in Table II.

It will also be seen from the Table that the individual organ averages show considerable differences; this is discussed below. The average solid organ concentrations for barbitone and phenobarbitone do not, however, differ appreciably. The small difference which they do show is statistically quite insignificant, i.e. is almost certainly due to random variation. The two barbiturates may therefore at this point be considered together.

Table II: Concentrations for Long-Acting Barbiturates

	Average Concentration in Solid Organs (% w/w)			*Concentration in Liver (% w/w)*			*Concentration in Brain (% w/w)*		
	Barbitone	*Phenobarbitone*	*Both Barbiturates*	*Barbitone*	*Phenobarbitone*	*Both Barbiturates*	*Barbitone*	*Phenobarbitone*	*Both Barbiturates*
Mean	·0188	·0196	·0191	·0217	·0178	·0201	·0174	·0144	·0161
Maximum	·0397	·0515*	·0515*	The maximum and minimum figures for the individual organs are not quoted, since the individual organ figures are not known for some of the average-organ maxima and minima.					
Minimum	·0031	·0072	·0031						

* See note to Table XV.

It is immediately apparent that the mean of the average concentrations in the solid organs is considerably greater than that for the other two groups (Tables IV and VI). A statistical calculation, comparing this mean with that for *all* barbiturates (0.0142%) by the method of single means,[8] shows that the difference is significant. ($t = 2.33$; this corresponds to a probability of *ca.* 0.026†; that is, the odds against this difference arising through random variation[9] are about 38 : 1.)

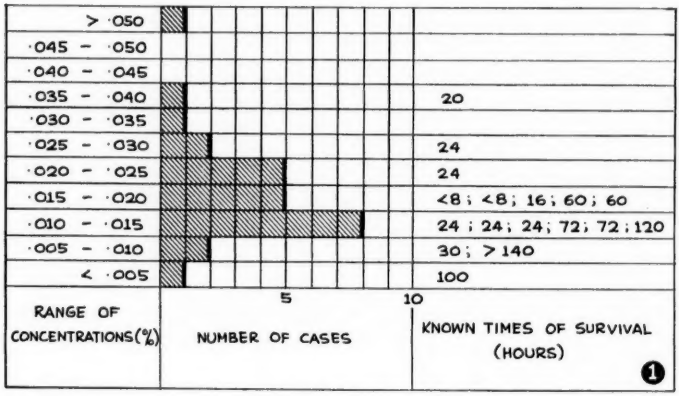

Fig. 1. Long-acting barbiturates.

† See note to Table X.

This result supports the generally accepted view that the long-acting barbiturates are less potent than the others, since it can safely be assumed that the amounts actually ingested bore no relation to the type of barbiturate used. Copeman[28] also concludes that barbitone and phenobarbitone are less toxic than the remaining barbiturates. Table III shows the calculated amounts present in the whole body on the basis of the average solid organ concentrations.

Table III: Estimated Quantities Ingested for Long-Acting Barbiturates

Solid Organ Concentration	*Male* (*Flesh Weight of 60 kg. Assumed*)	*Female* (*Flesh Weight of 50 kg. Assumed*)
Mean	11·5 g.	9·5 g.
Maximum	30·9 g.	25·7 g.
Minimum	1·8 g.	1·5 g.

These figures agree fairly well with those given by Wayne,[30] which have apparently been derived on a similar basis. Wayne gives the following minimum, median and maximum estimated fatal doses:

Barbitone: 2.0, 6.0 and 24.0 g.

Phenobarbitone: 1.6, 5.25 and 17.5 g.

The figures corresponding to the minimum concentrations probably represent less than the actual amounts ingested. It will be seen from Fig. 1 that, where the periods of survival are approximately known, these are nearly all long enough at the lower concentrations to make it unlikely that all the material originally absorbed will be recovered on analysis of the organs. This point is discussed below (section 6).

The maximum hypnotic oral doses are given in the British Pharmacopoeia as 0.6 g. for barbitone and 0.12 g. for phenobarbitone. In spite of the considerable difference in potency which these doses seem to indicate, the solid organ concentrations for the two drugs found here do not reflect this. They are, in fact, slightly higher on the average for phenobarbitone, but the difference is, as already mentioned, not significant. Taking the usual hypnotic oral doses as 0.30 g. barbitone and 0.10 g. phenobarbitone, the 'toxic' doses (according to the statement by Burger quoted above) would be 3-4.5 and 1-1.5 g. respectively. The results discussed here seem therefore to support Burger's statement for barbitone but hardly for phenobarbitone.

It is also of interest to note that Burger[10] quotes the toxic dose for the rabbit as 0.025% w/w barbitone and 0.015% w/w phenobarbitone. These figures are close to the average fatal concentrations in Man found here (Table III).

(*b*) *Intermediate-Acting Barbiturates.* This group numbers 28 cases, and the figures are summarized in Tables IV and V and in Fig. 2.

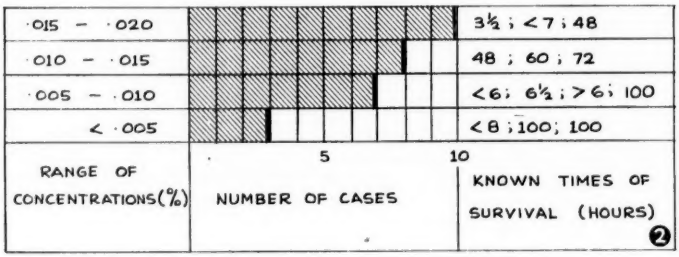

Fig. 2. Intermediate-acting barbiturates.

Table IV: Concentrations Found for Intermediate-Acting Barbiturates

	Average Concentration in Solid Organs	*Concentration in Liver, %*	*Concentration in Brain, %*
Mean	·0116	·0169	·0075
Maximum	·0191	·0329	·0141
Minimum	·0006	·0006	·0008

In calculating the figures given in Table V, Cases 1 and 56 are excluded, which seems justified in view of the combined occurrence there of long times of survival and very low analytically determined concentrations in the organs.

Table V: Estimated Quantities Ingested for Intermediate-Acting Barbiturates

Solid Organ Concentration	*Male (Flesh Weight of 60 kg. Assumed)*	*Female (Flesh Weight of 50 kg. Assumed)*
Mean	7·0 g.	5·8 g.
Maximum	11·5 g.	9·5 g.
Minimum (·0030%—Case 33)	1·8 g.	1·5 g.

Wayne[30] estimates 1.6 g. as a median fatal dose for amylobarbitone. It will be seen that this is lower relative to the figures in Table V than are his long-acting estimates relative to those in Table III.

(*c*) *Short-Acting Barbiturates.* This group numbers 19 cases, and the figures are summarized in Tables VI and VII and in Fig. 3.

Table VI: Concentrations Found for Short-Acting Barbiturates

	Average Concentration in Solid Organs	*Concentration in Liver, %*	*Concentration in Brain, %*
Mean	·0124	·0128	·0101
Maximum	·0331	·0281	·0362
Minimum	·0024	·0007	·0021

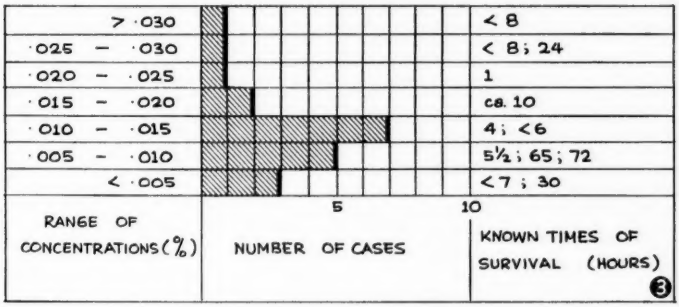

Fig. 3. Short-acting barbiturates.

Table VII: Estimated Quantities Ingested for Short-Acting Barbiturates (All cases included)

Solid Organ Concentration	*Male (Flesh Weight of 60 kg. Assumed)*	*Female (Flesh Weight of 50 kg. Assumed)*
Mean	7·4 g.	6·2 g.
Maximum	19·9 g.	16·5 g.
Minimum	1·4 g.	1·2 g.

Wayne[30] estimates 1.0(?) g. pentobarbitone and 1.2(?) g. quinalbarbitone as median fatal doses. These again are low compared with the figures in Table VII.

Groups (b) and (c). These two groups may be considered together. The only apparent difference between them is that, with the intermediate-acting but not with the short-acting group, there appears to be a 'ceiling' at a solid organ concentration of about 0.02%. In view, however, of the relatively small number of cases, this difference may not be real. If it is, the writer is not in a position to offer a plausible explanation for it.

As is to be expected from the way in which the data are used, there is no statistically significant difference between the average solid organ con-

centration for either group and the corresponding mean figure for all barbiturates.

In so far as the two sets of figures are comparable, the concentrations found here for the intermediate- and short-acting barbiturates agree with those of Copeman,[28] although his are average figures for all groups. In other previously reported cases of fatal poisoning by barbiturates in these two groups, the figures quoted fall within the limits shown in Tables IV and VI.[6, 7]

Table VIII: Therapeutic and Probable Toxic Doses of Barbiturates of Groups B and C

Barbiturate	*Published Hypnotic dose (grammes)*			*Average Adult Dose (Burger) (grammes)*	*Average Adult Dose* x 12½	*Toxic Dose for Rabbit (Burger) (% w/w)*
	Minimum	*Maximum*	*Authority*			
Allobarbitone..	·03	·20	BPC	·20	2·5 g	*
Amylobarbitone	·10	·55†	BPC	·20	2·5 g	·017
Butobarbitone	·06	·12	BPC	·075	ca. 1 g	·010
Cyclobarbitone	·20	·40	BPC	·15	1·9 g	*
Pentobarbitone	·09‡	·18‡	BPC	·15	1·9 g	*
Quinalbarbitone	·045‡	·18‡	BP	·15	1·9 g	*

BP: British Pharmacopoeia 1953.
BPC: British Pharmaceutical Codex 1949.
* No figure quoted.
† as amylobarbitone sodium.
‡ free acid equivalent to published doses of sodium salt.

In Table VIII are given the therapeutic doses, and the probable toxic doses on Burger's estimate,[3] of the barbiturates in groups (*b*) and (*c*). It will be seen that Burger's estimated figure agrees pretty well with the figures actually found (Tables V and VII).

The different dosages given for the barbiturates in these groups presumably signify a difference in potencies. The average solid organ concentration for each was therefore compared with the mean figure for the whole of groups (*b*) and (*c*). In the cases of amylobarbitone, butobarbitone and pentobarbitone, the figures were not appreciably different from the mean; in the case of quinalbarbitone the figure was less than the mean, but statistical calculation showed that the difference was not significant and might well be due to random variation; in the cases of allobarbitone and cyclobarbitone there were too few cases to make any significant comparison possible.

3. Distribution in the Body

Several conflicting statements have in the past been made about the segregation of barbiturates in different organs, especially in the brain and the liver. It must now be clear that many of these statements were based on

insufficient evidence, and on consideration of too few individual cases for safe generalization.

Thus, some confusion was caused by McNally,[11] who quoted a case[12] which seemed to indicate concentration of phenobarbitone in the brain. This led to the publication[5] of the results of a series of 5 cases of barbitone and phenobarbitone poisoning which showed no concentration in the brain. On the other hand, Adriani[13] states categorically:

'The brain, because of its high lipoid content and excellent blood supply, absorbs larger amount per unit weight than organs of a non-lipoid nature, or those with a poorer blood supply. This is especially true of barbiturates possessing high molecular weight alkyl substituents'.

It is, however, now generally agreed (more extensive evidence on the subject being available) that the distribution throughout the body is not in fact uniform. Thus, Maynert and van Dyke say:[14] 'Barbiturates are actually concentrated or localized in some tissues such as the liver and kidneys'. The same authors, and Butler,[15] found a positive and negative segregation, respectively, of barbitone in the brain. Raventós[16] quotes a number of figures (though most of these are for thiobarbiturates, which are not considered here) showing uneven distribution among the various organs. Finally, Wright (in a recent paper[7]) states:

'It is nevertheless generally agreed . . . that concentration of all barbiturate derivatives occurs in the liver and kidneys'.

He also gives the analytical results in a number of cases. These show a high concentration in the liver and a low one in the cerebrospinal fluid, taking the blood concentration as datum level.

Table IX: Segregation of Barbiturates in the Tissues

Class of Barbiturate	*Numbers of Cases*			
	Liver Concentration		*Brain Concentration*	
	Greater than Average	*Less than Average*	*Greater than Average*	*Less than Average*
Long-acting	14	5	7	17
Barbitone	8	3	7	7
Phenobarbitone	6	2	0	10
Intermediate-Acting	18	3	4	24
Short-Acting	9	4	7	10
Total: All Barbiturates ..	41	12	18	51

An examination of the data available here confirms broadly the statements of the more recent authors quoted above, and also enables us to amplify them in some particulars. If one takes the figures given in Table I and compares, case by case, the barbiturate concentration in the individual organs with the solid organ averages, it will be found that it is most

common for the liver concentration to be higher than average, and the brain concentration lower. The detailed results of this comparison are set out in Table IX.

The reality of this tendency was tested by statistical methods. The arithmetical differences between the liver concentrations and the average solid organ concentrations, and between the brain concentrations and the latter, were determined for each case, the means of these differences calculated, and tests for significance[8] applied to discover whether these means differed significantly from zero. The results of these tests are summarized in Table X.

Table X: Segregation of Barbiturates in the Tissues—Statistical Analysis of Results

Group		(1) *Solid Organ Average Concentration* *	(2) *Organ*	(3) *Mean Figure for Organ*	(4) *Ratios Organ Concentration ÷ Average Solid Organ Concentration* ‡	(5) $\bar{X}$ §	(6) *Calculated Value of t* **	(7) *Probability Corresponding to t Value and Number of Cases* **
All barbiturates ..		·0142	Liver	·0167	1·21	·00272	4·40	< ·001
			Brain	·0112	·80	·00290	4·80	< ·001
Long-acting	Barbitone	·0188	Liver	·0217	1·06	·00085	·90	Not significant
			Brain	·0174	1·01	·00067	·84	Not significant
	Phenobarbitone	(·0196) (·0151†)	Liver	·0178	1·15	·00266	1·68	·14
			Brain	·0144	·73	·00523	3·10	·013
Intermediate-acting ..		·0116	Liver	·0169	1·32	·00478	4·73	« ·001
			Brain	·0075	·74	·00350	5·02	« ·001
Short-acting		·0124	Liver	·0128	1·14	·00235	1·82	·096
			Brain	·0101	·78	·00312	1·48	·195

* See Tables II, IV and VI.

† Mean figure excluding 2 particularly high individual figures for which the corresponding liver figures are not available.

‡ These ratios are the means of the several ratios calculated separately for each case, and may therefore differ from the ratios of the figures in columns (3) and (1).

§ This column contains the means of the differences, calculated separately for each case: (average concentration in solid organs) minus (concentration in particular organ in question). This figure, and that given in column (4), show the degree to which there is a tendency to a positive or negative segregation in an organ. If there were no such tendency, then, for a large number of cases, the figure in column (4) would $\simeq 1$ and the figure $\bar{X}$ would $\simeq 0$.

** For a particular set of values, which have a certain degree of randomness given by the values themselves, and whose mean shows a certain positive or negative bias, the factor t is a measure of the probability that this bias could be due to the observed randomness. The probabilities are given in column (7). Obviously, the smaller this probability, the greater the probability that the observed bias is due to a real tendency to segregation and is not due to random variation.

The results shown in Table X may be summarized thus:

Taking all the barbiturates into account, there is an undoubted tendency for the liver concentration to be high, and for the brain concentration to be low, compared to the average for all solid organs. This confirms Wright's results.[7]

If one considers this tendency in detail for the different groups of barbiturates, one finds:

With *barbitone,* there is no evidence of a tendency to segregation in either organ. This is shown by the organ: average ratios in column (4) not differing appreciably from 1.

With *phenobarbitone,* there is probably a tendency for the liver concentration to be higher than, and almost certainly a tendency for the brain concentration to be lower than, the average.

With the *intermediate-acting barbiturates,* there is a most undoubted tendency towards high liver and low brain figures.

With the *short-acting barbiturates,* there is very probably a tendency for the liver concentration to be higher than average, and probably a tendency for the brain concentration to be lower than average.

Statistical calculations were also made using the differences between the means for the 2 organs of the ratios given in column (4) of Table X. These led to conclusions similar to those given above.

These results hardly support the second part of the statement by Copeman[28] that 'the concentration of barbiturate [any barbiturate, implied] in the liver is dependent upon the size of the dose ingested and may thus be regarded as a reasonable criterion of the dosage'. His further statement that 'the relative distribution must depend largely upon the individual constitution' also appears to be no more than partly true. These results also do not support the further suggestion by Wright[7] that certain barbiturates, e.g. pentobarbitone, appear in a higher concentration in the brain. This was examined by calculating the mean ratios shown in column (4) of the Table separately for each individual barbiturate. Wherever there were enough cases involving any particular barbiturate to give this mean any significance, it did not differ significantly from that for the whole group. In the particular case of pentobarbitone quoted by Wright, the mean (0.63) was, in fact, rather lower than the corresponding average for the group (0.78).

The data available do not, unfortunately, enable any comparison to be made with the results quoted by Raventós,[16] and those, e.g. of Brodie *et al.*,[17] which indicate localization of certain barbiturates (notably thio-barbiturates), but not of others, in body fat.

Table XI: Concentration in Cases Showing Anomalous Organ Segregation

		Long-Acting	*Intermediate-Acting*	*Short-Acting*
No. of Cases		7	3	8
Average Solid Organ Concentration	*Mean*	·0143	·0053	·0111
	Maximum	·0215	·0087	·0270
	Minimum	·0031	·0006	·0024

A separate examination was made of the figures for those cases in which the usual trend was reversed—in which, i.e. the liver concentration was lower than, and/or the brain concentration higher than, the solid organ

average. A few borderline cases were excluded by taking only liver concentrations less than 90% of, and brain concentrations more than 110% of, the solid organ average. Eighteen cases then remain for consideration (Nos. 1, 2, 5, 16, 21, 23, 32, 37, 40, 42, 52, 53, 54, 57, 59, 60, 62, 65, of Table I). Most of these are cases with low average solid organ concentrations: the figures for them are summarized in Table XI, and may be compared with the figures in Tables II, IV and VI.

Statistical calculations[18] were made on the differences between the mean figures shown in Table XI and the corresponding mean figures for the remaining cases (but excluding also the borderline cases excluded from Table XI). The comparisons were made in two groups: long-acting barbiturates in one, and the remainder in the other. (This course was considered justified since the mean average-organ concentrations for the intermediate- and short-acting groups do not differ significantly—see above. Table XI to justify comparison). The results of these calculations are shown in Table XII.

Table XII: Statistical Calculations on Cases Showing Anomalous Organ Segregation

Class of Barbiturate	*Number of Anomalous Cases* (N_1)	*Mean Value for Anomalous Cases*	*Number of Normal Cases* (N_2)	*Mean Value for Normal Cases*	*Calculated Value of Factor* t	*Probability*[9] *for Calculated Value of* t *and for* $n = N_1 + N_2 - 2$
Long-Acting	7	·0143	15	·0193	1·032	$\simeq 0{\cdot}3$
Intermediate- and Short-Acting	11	·0095	33	·0132	1·662	0·105

The results shown in Table XII may be interpreted as follows:

In the case of the long-acting barbiturates, although the mean concentration for anomalous cases is considerably less than that for the 'normal' cases, there is a large probability that the difference may be due to random variation, and it is therefore not significant. This result is perhaps only to be expected, since most of the anomalous long-acting cases were barbitone ones, and we have already seen that barbitone is unique in not being regularly segregated in the organs. Unfortunately, as there are only two phenobarbitone cases in this group, there is insufficient material for a calculation based on these alone.

In the case of the intermediate- and short-acting barbiturates, there is probably a connection between low average solid organ concentrations and relatively high brain and/or low liver concentrations.

In similar calculations based on a series of 21 cases, Copeman[28] finds some suggestion that the ratio $\frac{\text{Liver Concentration}}{\text{Kidney Concentration}}$ tends to be higher for

large than for small doses of barbiturates. As he takes the liver concentration by itself as a criterion of dosage (see above), he thence infers that there is a relatively greater excretion through the kidneys with low average-organ concentrations. It will be seen that, if the present tentative conclusions are correct, his statistical results may equally well be explained on the assumption that his kidney concentrations approximate to the solid organ average at all levels of concentration.

Since it is a reasonable *a priori* assumption that low average concentrations will be associated with long survival times, one is tempted to suggest that anomalous organ segregation will be found in cases of long survival. This suggestion is not, however, supported by the evidence. The point is discussed in section (6) below.

4. Sex Differences

Animal experiments made a number of years ago showed a sexual difference in susceptibility to barbiturates,[19] and Donatelli has stated[20, 21] that women are more resistant than men.

To test this point, statistical calculations were made on the mean average-organ concentrations for both sexes. While it is the case that this concentration is slightly higher for women (0.0152) than for men (0.0131), the difference is not statistically significant. Indeed, calculation shows that the probability of its being due to random variation is more than one-half. The available evidence, therefore, whilst it does not disprove Donatelli's statement, certainly does not support it.

Table XIII: Sexual Differences with Short-Acting Barbiturates

	Male	*Female*	*Both Sexes*
Mean Solid-Organ Average Concentration ..	·0135	·0112	·0124
Mean Liver Concentration	·0106	·0145	·0128
Mean Brain Concentration	·0114	·0088	·0101
$\frac{\text{Liver*}}{\text{Average}}$	0·86	1·35	1·14
$\frac{\text{Brain*}}{\text{Average}}$	0·90	0·64	0·77

* The figures in these lines are the means of the ratios (calculated separately for each case) $\frac{\text{Organ Concentration}}{\text{Average Solid Organ Concentration}}$ and may therefore differ from the ratios of the corresponding mean figures in the first 3 lines.

The mean average-organ, brain and liver concentrations, grouped according to sex, were also calculated for the 3 groups of barbiturates separately. Again no statistically significant differences between the average

organ figures for the two sexes were found. In the case of the short-acting barbiturates, however, some quite large differences in the extent of organ segregation appeared. The figures are shown in Table XIII.

It will be seen from Table XIII that, compared with the average solid-organ concentration, the liver concentration is low in the male and high in the female, and conversely for the brain concentration. The statistical significance was tested by comparison for the 2 sexes of the ratio $\frac{\text{Individual Organ Concentration}}{\text{Average Solid Organ Concentration}}$. These ratios were calculated individually for each case, and the significance of the difference between the means estimated for each of the pairs of groups $\left(\frac{\text{liver}}{\text{average}} \text{ male}; \frac{\text{liver}}{\text{average}} \text{ female}\right)$ and $\left(\frac{\text{brain}}{\text{average}} \text{ male}; \frac{\text{brain}}{\text{average}} \text{ female}\right)$.

In the case of the liver pair, $t = 2.36$; $p = 0.035$; i.e. the odds are about 29 : 1 in favour of the difference being real. In the case of the brain pair, $t = 1.125$; $p = 0.26$. This shows a slight balance of probability in favour of the difference being real.

The result for the liver figures must be accepted with reserve, because of the very small number of individual cases on which the calculation was based (6 male and 8 female), and because one of these 6 male cases showed an exceptionally low liver : average ratio (Case No. 32). Yet it is a fact that the liver : average ratio is throughout lower for males, whether calculated for all barbiturates or for each of the groups, although (except in the case of the short-acting barbiturates just discussed) the differences are small and statistically insignificant.

It seems safe to assume, therefore, that this tendency shown by Table XIII to a sexual difference in organ segregation with the short-acting barbiturates is a biological one. The difference cannot be connected with a low average solid organ concentration, as discussed in the previous section, since this is actually higher for males (Table XIII).

5. Age Differences

No statistically significant differences could be detected between old and young age groups (the borderline having been taken at various ages from 45-65), either in the average concentrations or in the degrees of segregation in the organs.

The suggestion by Donatelli[20] that men over 50 are more susceptible than men under 50 was also tested by statistical comparison of the mean concentrations of these two groups. The results did not support the suggestion. The average concentration in the over-50 group of males was, in fact, rather higher than that in the under-50 group, though the difference was small and statistically quite insignificant.

6. Period of Survival

The data to be examined under this heading are inevitably scanty since, not unnaturally, the periods of survival are rarely known with any accuracy.

The mean periods of survival, where known, were first calculated separately for the 3 groups and are shown in Table XIV. Although the mean figure is actually greater for the intermediate-acting than for the long-acting group, calculation showed that the difference between them is statistically quite insignificant, and is probably due to random variation. A test of significance was therefore applied to the difference between the means for the short-acting group and for the long-acting and intermediate-acting groups taken together (52.7 hours). This difference was just significant; it may therefore be assumed that survival times tend to be less with the short-acting group.

It was also suggested above that we may expect to find that low concentrations in the tissues are associated with long periods of survival. This association, if it exists, will be due to 2 factors:

1. A small initial dose will take longer to kill than a large one;

2. The longer the period of survival, the greater the loss of barbiturate by excretion and metabolic breakdown, and the less will be found on analysis. (According to Raventós,[16] the rate of disappearance from the blood varies from less than 4% per hour for the long-acting barbiturates to 10–15% per hour for the short-acting ones).

There appears however to be no way of distinguishing between the effects of these 2 factors with the data available.

It may perhaps be mentioned here that several cases (not included in Table I) have been investigated in this Laboratory in which, from the history, there was every reason to suspect barbiturate poisoning, but in which no barbiturate could be detected in the organs. It is noteworthy that in most of these cases the deceased survived for several days. Fisher[6] may be quoted on this point:

> 'On the other hand, barbiturates share with carbon monoxide and alcohol the property of producing irreversible asphyxial damage to the brain and then being partly or completely destroyed before death ensues'.

Copeman[28] also states that in cases of long survival death may be due to secondary effects.

Statistical tests for correlation between the survival time and several other variables were made in several ways. The other variables were the average organ concentration, the degree of segregation in the liver and the degree of segregation in the brain.

The calculations were made separately for each of the 3 groups of barbiturates. This was done:

1. By calculation of the product-moment coefficient of correlation.[22] This calculation can, of course, be applied only when the periods of survival can be given an at least approximate numerical value. There are, however,

a number of cases in which the periods are known only by their upper or (rarely) lower limits. The inclusion of these cases is desirable, if possible, in order to increase the data. In an attempt to do this, calculations were made in 3 further ways:

2. Spearman's ranking correlation coefficient[23] was calculated, using all available data.

3. A few calculations were also made by dividing the average organ concentrations into pairs of groups corresponding to values of the survival time greater or less, respectively, than the median, and applying the t test for significance to the differences between each pair of concentration means.

4. As the numbers of individual cases available for calculation were very small in both the intermediate-acting and short-acting group, calculations were also made on the cases in these groups combined as follows: The mean concentrations for the 2 groups are very nearly the same (Tables IV and VI), but the mean period of survival for the intermediate-acting group is 2.2 times that for the short-acting group. The short-acting periods of survival were therefore multiplied by 2.2, and the 2 groups then treated as one.

The product-moment coefficients of correlation for periods of survival and average organ concentrations are shown in Table XIV, as are also the results of applying tests of significance to these coefficients. It will be seen that there is a negative correlation varying from scarcely to just significant. This may be taken to mean broadly that the expected tendency for survival times to increase with decreasing average organ concentration almost certainly exists, except possibly in the short-acting group, but that it is all but masked by variations in individual susceptibility.

Table XIV: Time of Survival and Correlation with Concentration

Barbiturate Group	*Long-Acting*	*Intermediate-Acting*	*Short-Acting*	*Intermediate- and Short-Acting (Grouped as explained in the text)*
No. of cases (N)	13	9	8	17
Average period of survival (hours)	47·5	60·0	26·9	60
Coefficient of correlation with average organ concentration	—·44	—·63	—·45	—·49
Calculated value of t	1·62	2·12	1·23	2·15
Value of probability corresponding to values of N and t shown above	·14	·07	·26	·05

The figures for the calculations made under headings (2) and (3) above are not quoted, but they were generally in agreement with the results shown in Table XIV.

Somewhat surprisingly, in view of the results discussed in section (3), there was no significant degree of correlation, however calculated, between survival times and the degree of organ segregation. This might perhaps have been expected because of:

1. The association shown in section (3) probably to exist between anomalous organ segregation and low average-organ concentration;

2. The slight degree of correlation just discussed between concentration and survival times.

Such a correlation has also been claimed by previous authors. Adriani[13] states:

'The brain retains the barbiturate longer than other tissues and apparently exerts less destructive action upon it than other tissues'.

Wright[7] gives a series of figures for several cases which shows a tendency for the liver: blood ratio to decrease with increasing survival time, and states:

'It is apparent that shortly after ingestion of barbiturates quite high concentrations are found in the liver, whereas at longer intervals after ingestion these levels are of the same order as in blood'.

(Wright's 'basic' concentrations are of course for blood and not organ averages, as here. It seems however safe to treat his and those here as equivalent, as there is a good deal of evidence that they run parallel, e.g. Raventós[16]).

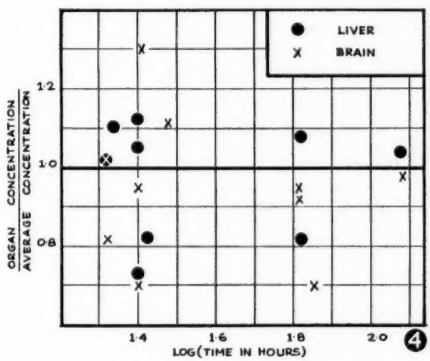

Fig. 4. Long-acting barbiturates. Segregation and survival.

One may assume that the absence of correlation here is due to the combined randomnesses of the segregation-concentration and concentration-time associations. The way in which organ: average ratios apparently vary quite randomly with survival times is shown in Figs. 4-6. (There is no theoretical reason for plotting the times on a logarithmic scale in these figures; this was done merely to space the points conveniently). With one exception, it is obvious from the figures that the points show no apparent

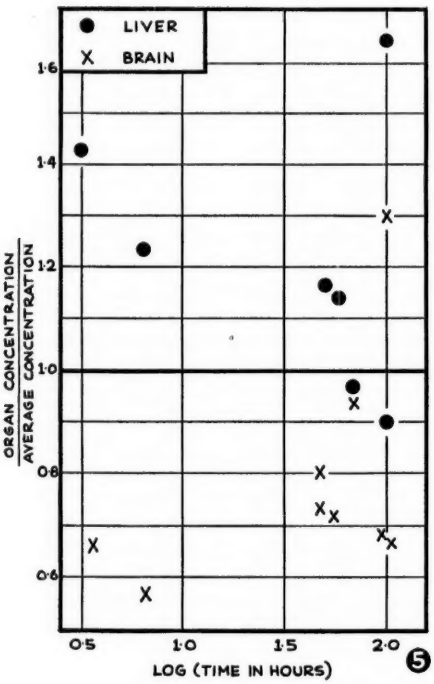

Fig. 5. Intermediate-acting barbiturates. Segregation and survival.

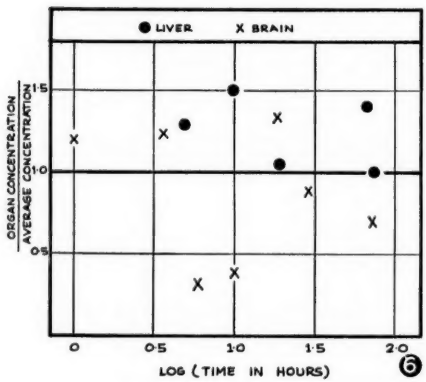

Fig. 6. Short-acting barbiturates. Segregation and survival.

trend. The exception is the brain : average ratios for the intermediate-acting group, which tend to rise with increasing time. Closer examination shows, however, that this tendency really depends on only 2 points at the lower left-hand corner of the figure; one can therefore hardly assume its reality. The correlation coefficient in this case was 0.54. This, although it is by far the largest coefficient, either positive or negative, occurring in the time-segregation series, is not statistically significant.

This finding therefore does not support Wright's further attractive suggestion : [7]

'Estimation of barbiturates in the liver thus gives useful information of the time elapsing between ingestion of the drug and death'.

Moreover, even if further data, as they become available, prove that the trend shown by Wright's figures is real and not fortuitous, it seems probable that it would be rash to attempt in any given case the estimation of survival times from the known liver : average or liver : blood ratios.

7. Concentration in the Urine

It is generally agreed that all the barbiturates undergo metabolic breakdown in the body, with the exception of barbitone, which is excreted unchanged.[17, 24-26] It is clear, however, from the occurrence with all barbiturates of a measurable amount in the urine whenever a toxic amount is present in the organs (Table I) that Tatum[27] is correct in stating that for any barbiturate there is a renal threshold, above which it is excreted unchanged. That this occurs, however, only with dangerously large doses, appears from the figures given by Maynert and van Dyke.[14] They give the percentages excreted unchanged after therapeutic doses as zero or negligibly small for most of the more rapid-acting barbiturates.

Needless to say, the present study adds nothing to the already large but by no means yet complete volume of work on the metabolic fate and degradation products of the barbiturates.

The urine percentages shown in Table I were expressed as a proportion of the average solid-organ concentration in each case, and the ratio (designated here by R) examined in conjunction with the other quantities and ratios already discussed to discover whether any significant regularities or trends were apparent.

No apparent association between the value of R and sex, age or extent of organ segregation could be detected. Correlation of R with survival time might well be interesting, but unfortunately very few cases were available in which both were known. A graphic plot of the two quantities suggested that their association is completely random, but nothing can really be said on this point without more data.

Certain regularities were, however, disclosed by a comparison of R with the average organ concentrations. The results of this are shown in Table XV. Certain points of interest emerge from the Table. As is to be

Table XV: Statistics of Urine Concentrations

Barbiturate	No. of Cases	Concentration in Urine* (mg.).100 ml.)			Urine Concentration* / Average Organ Concentration (R)			R for Average Organ Concentrations		Coefficient of Correlation of R and Average Organ Concentration	Corresponding Value of p (i.e. Probability that apparent correlation is due to chance)
		Mean	Max.	Min.	Mean	Max.	Min.	Less than Median	Greater than Median		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Long-Acting Whole Group	16	51			2·93			3·23	2·62		
Barbitone	10	57	104	15	3·00	5·69	1·10	2·92	3·07	≃ 0	
Phenobarbitone	6	41	71	20	2·82	6·01	·49†	4·38	1·24	—·83§	<·001§
Intermediate-Acting Whole Group	17	21		5‡	2·35		·26‡	3·74	1·21	—·69	<·01>·001
Amylobarbitone	10	20	29	6	2·15	5·38	·51	2·65	1·66		
Butobarbitone	6	28	61	6	3·06	6·41	·29	3·76	2·36		
Short-Acting Whole Group	11	28			1·71			·77	2·82	—·73	<·02>·01
Cyclobarbitone	2	59	95	24	2·81	3·51	2·10				
Pentobarbitone	5	10	38	3	1·18	2·05	·36	1·26	1·51		
Quinalbarbitone	4	31	112	0·2	1·82	5·49	·03	·50	3·14		

* In cases where both ante-mortem and post-mortem urine samples were available, the figure quoted and used is that for the post-mortem sample.

† This exceptionally low value of R for a long-acting barbiturate occurred in the case (No. 19) already mentioned as being that with the highest recorded concentration in the organs (·0515%, phenobarbitone). In no other case in this group is the value of R less than 1·10. Case No. 19 was that of a man whose body had lain for several weeks in the water.

‡ Figure refers to allobarbitone (one case).

§ Phenobarbitone grouped with intermediate-acting barbiturates in calculating these figures. For this purpose, the phenobarbitone average-organ concentrations were multiplied by $\frac{\text{average intermediate-acting organ concentration}}{\text{average phenobarbitone organ concentration}}$ — that is, by ·0116/·0196 (Tables II and IV).

expected, there is a decrease in the proportion of barbiturate excreted unchanged as we pass from the long-acting to the short-acting groups (column 5). In view, however, of the proven metabolic breakdown of the quicker-acting barbiturates, one might have expected the decrease to be more pronounced. Indeed, of the differences between the group values in column 5, those between the long-acting and the intermediate-acting, and between the intermediate-acting and the short-acting groups, are statistically quite insignificant, and the greatest difference—that between the figures for the long-acting and short-acting groups (2.93 and 1.71)—is barely significant ($t=1.88$; $p<0.1$, >0.05); i.e. the statistical evidence does not provide adequate proof that these differences are not due to random variation.

If, however, we assume that they are *probably* real, it may be concluded that, although the shorter-acting barbiturates may normally be metabolized without appreciable excretion of the unchanged drug, with large doses renal excretion is a more important means of elimination than is metabolic breakdown. Copeman[28] also considers the question of the relative importance of renal excretion, though without making a distinction between the different groups of barbiturates. He cites Webster[31] as stating that the larger the dose the less the relative percentage excretion, but adds that this statement does not seem to be borne out by his own results. On the other hand, he infers tentatively from his own liver and kidney concentrations that renal excretion is the greater, the lower the average concentration. This appears to agree with rather than to contradict Webster. However, it was suggested above (section 3) that Copeman's liver and kidney figures do not necessarily lead to the conclusion which he draws from them. In any case, the findings discussed in the following paragraphs suggest that, if all the barbiturates are considered together, no valid conclusions can be drawn about the percentage of renal excretion.

Some points of interest appear if one compares the values of R for each group of barbiturates, and for high and for low average organ concentrations respectively. (Columns 8 and 9, where the values of R are given for average organ concentrations less than, and greater than, respectively, the median value). The proportion of barbitone excreted is, on the average, practically the same whether the average organ concentration is high or low. This is to be expected. As is also to be expected, the proportion of the short-acting barbiturates excreted in the urine is smaller for low than for high average organ concentrations. What, however, might not have been expected is the fact that, with both phenobarbitone and the intermediate-acting group, the proportion excreted unchanged is greater with *low* average organ concentrations.

These last findings are illustrated graphically in Figs. 7 and 8, and are given numerical expression by the coefficients of correlation between the

values of R and the average organ concentrations (column 10).* The coefficients appearing in this column are statistically highly significant, as is shown by the corresponding probabilities (column 11). This may be taken to mean that the trends are undoubtedly real and are not accidents of random variation. These conclusions were also verified by statistical analysis of the differences between the pairs of mean values of R for organ concentrations less than median and greater than median. These differences were also highly significant statistically.

The writer cannot offer any real explanation of this anomalous result with phenobarbitone and the intermediate-acting group. Purely speculative suggestions can be made, such as that the rate of metabolic breakdown is proportional to a power greater than 1 of the concentration of metabolite, so that with a high concentration proportionally less time is available for excretion; or that there is an upper limit to the rate of renal excretion as

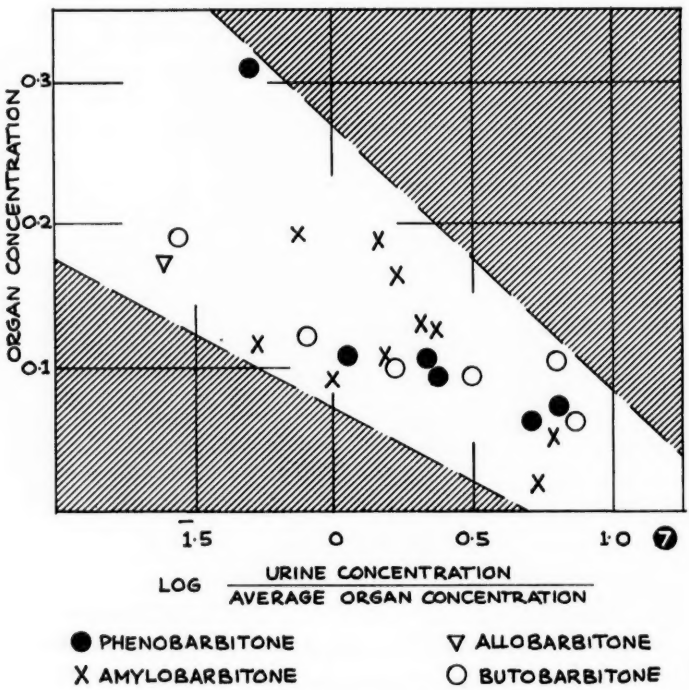

Fig. 7. Intermediate-acting barbiturates and phenobarbitone.

* The coefficient of correlation may have a value between −1 and +1, either extreme value indicating complete correlation. A negative value of the coefficient occurs when high values of one variable are associated with low values of the other.

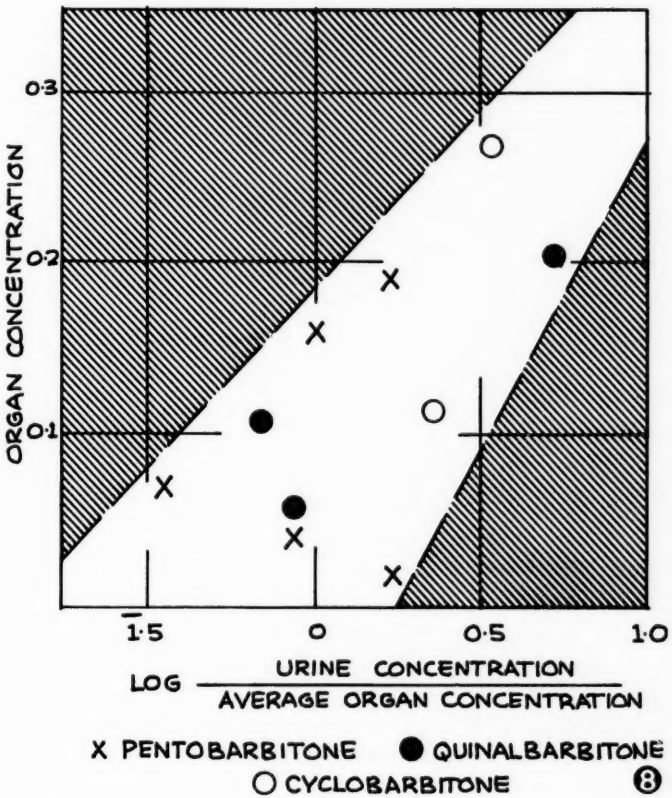

Fig. 8. Short-acting barbiturates.

well as a threshold, so that when the concentration is high enough a proportionately greater amount remains to be metabolized. The writer does not, however, know whether either of these speculations could be supported on medical grounds.

8. Conclusions

i. The highest concentration of barbiturate which can be reached in the tissues before death ensues appears to be about 0.04-0.05% for the long-acting barbiturates, and about 0.03% for the others.

ii. The mean tissue concentrations for all the cases examined were: long-acting, 0.0191%; intermediate-acting, 0.0116%; short-acting, 0.0124%.

iii. On the basis of the results discussed, it may be tentatively assumed that the minimum lethal dose for any barbiturate is between 1-2 g., and

the average lethal dose about 10 g. for the long-acting group and about 6 g. for the others.

iv. Barbitone appears to be evenly distributed throughout the body. There is probably a tendency for phenobarbitone, and almost certainly a tendency for the other barbiturates, to show a higher concentration than the body average in the liver, and a lower concentration in the brain. This tendency is least marked where the body average is low. It also appears to be less marked with men than with women, especially in the case of the short-acting group.

v. Given the amount ingested (or recovered) *or* the period of survival in any given case, no conclusion can be drawn about the other variable. The correlation between these 2 variables is all but obscured by variations in individual susceptibility.

There is also no significant correlation between the period of survival and the degree of positive or negative segregation in the brain or liver.

vi. After toxic doses, all barbiturates are excreted in the urine. With barbitone, the ratio of urine to tissue concentration is approximately constant.

With short-acting barbiturates, it is less for low than for high tissue concentrations; this is to be expected if elimination is normally through metabolism, with renal excretion taking place only above a threshold concentration.

With phenobarbitone and the intermediate-acting barbiturates, however, the ratio of urine to tissue concentrations is greater for low than for high tissue concentrations. This can be explained only speculatively.

The writer's thanks are due, and gladly expressed, to: Mr. E. B. Parkes, M.Sc., F.R.I.C., Director of this Laboratory, for permission to submit this paper for publication; the chemical staff of this Laboratory, whose painstaking work has made this study possible; Dr. Frank George, Department of Psychology, Bristol University, for invaluable elementary advice in statistical methods; and Dr. F. E. Camps, Reader in Forensic Medicine at the London Hospital Medical College, for the helpful interest he has shown in the work.

References

1. Valov, P. (1946): Ind. Eng. Chem. (Anal. Ed.), **18**, 456.
2. Lilliman, B. (1950): Analyst, **75**, 626.
3. Burger, A. (1951): *Medicinal Chemistry*, p. 118. Interscience Publishers.
4. Zwikker, J. J. L. and Steenhauer, A. J. (1940): Chem. Abs., 4158.
5. Andrew, R. L. and Neubauer, L. G. (1947): Analyst, **72**, 21.
6. Fisher, R. S. (1949): New Eng. J. Med., **240**, 395.
7. Wright, J. T. (1955): Quart. J. Med., **24**, 95.
8. Chambers, E. G. (1952): *Statistical Calculations for Beginners*, p. 37. Cambridge University Press.
9. Fisher, R. A. and Yates, F. (1953): *Statistical Tables for Biological, Agricultural & Medical Research*, 4th ed. Edinburgh and London: Oliver and Boyd.
10. Burger, A. (1951): *Loc. cit.*, p. 121.

11. McNally, W. D. (1937): *Toxicology,* p. 721. Chicago: Industrial Medicine.
12. Wright, H. N. (1929): Arch. Int. Med., **43,** 85.
13. Adriani, J. (1946): *The Chemistry of Anaesthesia,* p. 232. Oxford: Blackwell Scientific Publications.
14. Maynert, E. W. and van Dyke, H. B. (1949): Pharmacol. Rev., **1,** 217.
15. Butler, T. C. (1950): J. Pharmacol., **100,** 219.
16. Raventós, J. (1954): J. Pharm. (London), **6,** 217.
17. Brodie, B. B. *et al.* (1953): J. Pharmacol., **109,** 26.
18. Chambers, E. G. (1952): *Loc. cit.,* p. 41.
19. Holck, H. G. O. *et al.* (1937): J. Pharmacol., **60,** 323.
20. Donatelli, L. (1947): Chem. Abs., 3212.
21. Donatelli, L. (1947): Chem. Abs., 6334.
22. Chambers, E. G. (1952): *Loc. cit.,* p. 52.
23. Chambers, E. G. (1952): *Loc. cit.,* p. 69.
24. Williams, R. Tecwyn (1949): *Detoxication Mechanisms,* p. 218. London: Chapman & Hall.
25. Maynert, E. W. and van Dyke, H. B. (1950): J. Pharmacol. (Abs.), **98,** 22.
26. *Rep. Prog. Appl. Chem.* (1953): **38,** 155.
27. Tatum, A. L. (1939): Physiol. Rev., **19,** 472.
28. Copeman, P. R. v. d. R. (1953-4): J. Forensic Med., **1,** 271.
29. Thrower, W. R. (1953-4): J. Forensic Med., **1,** 106.
30. Wayne, E. J. (1953-4): J. Forensic Med., **1,** 172.
31. Webster, R. W. (1930): *Legal Medicine and Toxicology.* Philadelphia: W. B. Saunders Co.

Notes and News

American Academy of Forensic Sciences

The American Academy of Forensic Sciences 10th Annual Meeting (27–28 February, 1 March 1958) was held at the Hotel Carter, Cleveland, Ohio.

An interesting feature of the meeting was a symposium devoted to *What's New in Forensic Science?*

The sectional meetings included contributions on *Infanticide* (Dr. Lester Adelson), *Fatal Penicillin Anaphylaxis* (Dr. A. Rosenthal) and *Evaluation of the Fractured Hip, Contributory or Non-contributory Factors in Death* (Dr. J. E. Campbell).

There were also symposia on the *Use of Statistics in Court Room Testimony* and *Investigation of Sudden, Unexplained or Obscure Deaths.*

There was a special session on *Modern Concepts in the Investigation of Aircraft Fatalities.*

An important session included the following topics:

Determination of Time of Death from External Factors (Drs. Herbert P. Lyle and Frank P. Cleveland); *Post-Mortem Biological Changes* (Dr. Walter W. Jetter) and *Determination of Time of Death by Measurement of Heat Loss from the Body* (Drs. Frank P. Cleveland and Herbert P. Lyle).

* * *

British Association in Forensic Medicine

Dr. Francis E. Camps, Reader in Forensic Medicine (University of London), at the London Hospital Medical College, has been appointed President of the British Association in Forensic Medicine.

* * *

E. & S. Livingstone of 15–17 Teviot Place, Edinburgh 1, have just issued a new catalogue which gives details of new and forthcoming publications.

A copy of this catalogue will be sent to anyone interested on application to E. & S. Livingstone Limited.

The Royal Medico-Psychological Association

MAUDSLEY BEQUEST

A Two-day Lecture Course has been arranged at The Royal Society of Medicine, 1 Wimpole Street, London, W.1 on Monday and Tuesday, 10 and 11 February, 1958.

PROGRAMME

First Day: 10 *February*, 1958

10.00 a.m.—11.15 a.m.: Work and Social Therapies in Mental Hospitals (Dr. Rudolf Freudenberg).

11.30 a.m.—12.45 p.m.: Community Treatments of Mental Illness (Dr. Duncan MacMillan).

2.00 p.m.—3.15 p.m.: Psychiatric Pioneers and Precursors (Dr. Alexander Walk).

3.30 p.m.—4.45 p.m.: The Treatment of Early Schizophrenia (Dr. W. Mayer-Gross).

Second Day: 11 *February*, 1958

10.00 a.m.—11.15 a.m.: Treatment in Neurosis Centres (Dr. Louis Minski).

11.30 a.m.—12.45 p.m.: The EEG and Psychiatric Research (Professor Martin Roth).

2.00 p.m.—3.15 p.m.: Psychopathic States and the EEG (Dr. Desmond Pond).

3.30 p.m.—4.45 p.m.: The Treatment of Psychosomatic States (Dr. Denis Leigh).

Each lecture will be followed by questions from the audience.

Admission is by ticket and is free to members of the Royal Medico-Psychological Association; the fee for the course to other doctors and psychologists is £1 5s. (single days 15s. each).

Application for tickets should be made as soon as possible to The Registrar, Royal Medico-Psychological Association, 11 Chandos Street, Cavendish Square, London, W.1.

Reviews of Books

BLOOD ALCOHOL

Blutalkohol: Die Wissenschaftlichen Grundlagen der Beurteilung von Blutalkoholbefunden bei Strassenverkehrsdelikten. By Dr. Herbert Elbel and Dr. Franz Schleyer. 2. Auflage, Vollig Neubearbeitet. 1956. (Pp. 222 + Index. DM 27.-). Stuttgart: Georg Thieme Verlag.

This is a very comprehensive review of all aspects of the significance and deter-

mination of alcohol in the blood. There is a detailed account of the absorption of alcohol, its distribution in the tissues of the body, its oxidation and the influence of hormones and vitamins.

The discussion of the alcohol estimation in blood obtained *post mortem* includes reference to the important work of Gormsen, who has demonstrated that yeasts as well as bacteria may produce ethyl alcohol after death—a factor which may severely vitiate the interpretation of the chemical findings on putrid cadavers.

There is also an important section dealing with blood alcohol findings in relation to traffic accidents.

This excellent monograph concludes with a very detailed and extensive bibliography. There is also an adequate subject index.

Medical Jurisprudence and Toxicology: Glaister

Medical Jurisprudence and Toxicology. By John Glaister, J.P., D.Sc., M.D., F.R.S.E., F.R.F.P.S. (Glasg.). 1957. 10th ed. (Pp. 693 + Index. With 225 illustrations, 72 in colour. 47s. 6d.). Edinburgh and London: E. & S. Livingstone Ltd.

The 10th edition of this standard reference work has given the author the opportunity to make substantial changes in the text, thus bringing the volume up to date.

In his preface, Professor Glaister refers to the following important addenda: The Matrimonial Causes Act, 1950; the Corneal Grafting Act, 1952; the Prevention of Crimes Act; 1953, the Coroners' Rules (1953) (No. 205); the Medical Act, 1956; the Dentists Act, 1956; the Sexual Offences Act, 1956; the Road Traffic Act, 1956; the Homicide Act, 1957; recent changes in the law, together with relevant cases, connected with the liability of hospitals and nursing homes; surgical sterilisation; the acid-phosphatase test for seminal fluid; the anti-human globulin test for human blood; recent trends relating to the treatment of barbiturate poisoning, and the antihistamine compounds.

On page 392 a valuable Table is published setting out the criteria for the differentiation of newly born infants, in relation to their age at birth. The Table includes the length, the weight and the ossification centres at 7 months, 8 months and 9 months.

The importance of the way in which the sex of the child affects the ossification centres is to-day well established and generally recognized. The value of the Table would, therefore, be increased appreciably if it is amplified to include sex differences, which may be considerable, e.g. the centre at the lower end of the femur may appear in the female some 4 weeks earlier than it does in the male child.

In dealing with the difficult problem of live birth, Professor Glaister recapitulates modern research on the microscopic appearances of the foetal lung. This investigation has lost all value in differentiating live from still births.

The author readily points out that the histological criteria are not of assistance to 'the medico-legal practitioner or to the legal authorities in deciding whether or not there is sufficient evidence of live birth on which to found a charge of infanticide' (p. 381).

The misleading photomicrographs of the lungs from newly born infants who have breathed and who have been stillborn, have, very properly, been eliminated from the Chapter on *Infanticide*.

An important new development reported in this latest edition is the anti-human globulin test for human blood. Its role as a substitute for the precipitin test for medico-legal purposes has not yet been established. It appears to have the merit of being a more specific test. The end-point is very simple and clear, viz. inhibition of agglutination of the red cells under the conditions of the test. An extensive investigation into the behaviour of the blood of the higher primates is, however, required before its medico-legal applications can be fully evaluated. Unless the primates can be excluded, the test will be valueless in many parts of the world.

The caution with which Professor Glaister advises the use of the acid phosphatase test for the detection of a seminal stain will be endorsed by all forensic practitioners. Glaister has found it a useful 'sorting test', and he is of the opinion that it should not be relied upon by itself 'as definite evidence of the presence of a seminal stain for court purposes' (p. 414).

This new edition will undoubtedly continue to enjoy a considerable popularity among students as well as the multitude of practitioners who find themselves constantly involved in forensic problems.

Gerichtliche Geburtshilfe

Gerichtliche Geburtshilfe. By Prof. Dr. H. Naujoks. 1957. (Pp. 247). Stuttgart: Georg Thieme Verlag.

Contents: 1. Juristische Fragen um die Geburt. 2. Die legale Schwangerschaftsunterbrechung. 3. Die Abtreibung. 4. Die Kindestötung. 5. Trauma und Schwangerschaft. 6. Der unvermutete, plötzliche Tod in Schwangerschaft, Geburt und Wochenbett. 7. Das geburtshilfliche Vaterschaftsgutachten. 8. Die ärztliche Schweigepflicht in der Geburtshilfe. 9. Einwilligung und Aufklärung bei geburtshilflichen Massnahmen. 10. Der sogenannte „Kunstfehler" in der Geburtshilfe. 11. Irrtümer und Fehler in der Geburtshilfe und ihre Strafbarkeit. 12. Der Geburtshelfer vor Gericht.

Professor Naujoks' book is in German. It concerns itself in a very practical manner with the forensic problems arising out of pregnancy and labour. The volume would undoubtedly gain a considerably greater audience if it were translated into English. The wealth of clinical experience which is contained in this monograph deserves attention beyond the limited German-speaking populations.

For those familiar with the author's language, the detailed list of chapter headings provided will indicate adequately the scope of this volume.

Abortion

Spontaneous and Habitual Abortion. By Carl T. Javert, M.D. 1957. (Pp. 408 + Index. Illustrated. $11.00). New York: McGraw-Hill Book Company, Inc.

Contents: Part I. Introduction. *Part II.* Pathology. *Part III.* Clinical Obstetrics. *Part IV.* Psychosomatology. *Part V.* Epilogue.

Taussig's monumental work on abortion has long needed a sequel to keep the non-specialist practitioner informed in this important field of medical practice.

Professor Javert has made a special study of the numerous aspects of abortion and is particularly well qualified to fill in the 20-year gap which has occurred since Taussig's book was first published.

The author creates a sound basis for his discussion by traversing the physiology of normal pregnancy and then dealing comprehensively with the pathological conditions which may arise in the uterus, the ovary, the placenta and the foetus.

The forensic practitioner will be particularly interested in the section dealing with the indications for therapeutic abortion and the incidence of spontaneous abortion. A special chapter is devoted to the medico-legal aspects of this problem, from the disposition of still-born infants and foetuses to the evaluation of physical and psychic trauma as etiological factors in interrupting pregnancy. Particularly instructive is the hypothetical case of abortion, alleged to have been caused by emotion, fright and stress, argued before a group of lawyers attending a course of instruction arranged by the New York Law-Science Institute.

The numerous clinical illustrations are supplemented by very lively line drawings which must surely be a unique feature in a work of this kind. A very comprehensive bibliography, author index and subject index conclude what must surely become a standard work of reference in the post-Taussig period.

Investigation of Death

The Investigation of Death. By Donald Karl Merkeley, M.D., Med. Sc.D. (Forensic Medicine). 1957. (Pp. 133 + Index. With 33 Figs. 34s.). Oxford: Blackwell Scientific Publications.

The author is a pathologist and Honorary Lecturer in Forensic Pathology to the State College of Washington. He was formerly Pathologist, Royal Canadian Mounted Police. He has therefore had an extensive experience in the investigation of the causes of death, particularly as this relates to police work.

His monograph is a contribution to *The Police Science Series* and is written with an eye on the police officer who is, *inter alia*, called upon to assist in the investigation of death.

On important chapter is devoted to *Identification* (a chapter of interest and value to the medico-legal pathologist as well).

The simple account of *The Signs of Death* contains a useful diagram (Fig. 6, p. 36) setting out graphically the relationship between the various changes occurring in the body after death and which may be of assistance, in a general way, in fixing the approximate time of death.

The chapter on *Asphyxial Deaths* is marred by the perpetuation of the myth (exploded in recent years) that an indicative sign is to be found in the persistence of fluid blood after death. It is well established that in death from almost any cause the blood becomes

liquid a short time after death and then remains in this state.

It is also fallacious to rely on petechial haemorrhages, especially in dependent areas, as a specific sign suggesting an asphyxial mode of death. Gordon's researches have clearly established that petechiae are a non-specific sign and occur in death from almost any cause. In the case of dependent areas, the force of gravity may well produce petechiae.

Cyanosis is undoubtedly a reliable sign of oxygen lack (asphyxia) in the living. It has, unfortunately, no merit as a pathological sign. It is a clinical observation and the term should be expunged from the vocabulary of the forensic pathologist.

The chapter on *Gunshot Wounds* can be read with profit by the medical practitioner involved in cases of this kind. The illustrations are particularly instructive and effective.

In dealing with *Blood Stains,* it should be mentioned that the precipitin test, as routinely performed in the laboratory, is not uniquely distinctive of human blood. The test is positive for all primates and this may introduce difficulties, in certain parts of the world, where monkeys and apes are prevalent.

A short but practical chapter on *Toxicology* deals with the common poisons (ethyl alcohol, carbon monoxide and barbiturates).

This little volume is attractively produced, well illustrated and should prove of great interest to all those concerned with an introduction to the investigation of death.

Forensic Psychiatry

Psychiatry and the Criminal. A Guide to Psychiatric Examinations for the Criminal Courts. By John M. Macdonald, M.D. 1958. (Pp. 213 + Index. 42s.). Oxford: Blackwell Scientific Publications.

Psychiatric texts which confine themselves to the problems which arise in our courts, are few and far between. Professor Macdonald's volume is therefore particularly welcome, as it makes a significant addition to the scanty literature in this field.

The psychiatric examination of accused persons is recognized as an important feature of many cases with which the law is concerned. Some practitioners deliberately avoid being involved in work of this kind. There is an understandable resentment of the tactics of which the medical expert is sometimes the victim, when confronted by an astute legal adversary. The medical profession, however, has a special duty to assist the court, in the interests of justice, and Professor Macdonald's monograph should be an important way in which the expert witness can fortify himself for the exacting task of giving medical testimony, especially in the psychiatric field.

The chapters on *Amnesia* and *Epilepsy and the Electroencephalogram* are particularly useful and instructive. The chapter on *Alcoholism and the Law* covers a much wider field than is generally the case. The author lays a sound biochemical basis for an appreciation of the pharmacology of intoxication and stresses the extraordinarily great individual variation in the subject's reaction to a given concentration of alcohol. In discussing the reliability of chemical tests for intoxication (pp. 134-136) he draws attention, very properly, to the various ways in which alcohol may be produced in the body after death by bacteria (to which should be added fungi) and putrefaction. The way in which the diffusion through the stomach wall after death may increase the concentration of alcohol in the blood in distant sites is also emphasized.

The author draws attention to a point which is often overlooked, viz. that the symptoms of intoxication are more marked when the blood alcohol concentration is rising than when it is falling; indeed, at the same blood alcohol level, the same subject may be drunk at one time and perfectly sober a few hours later.

He also disposes of the contention that an analysis of the urine is reliable as a sole index of the blood alcohol level (p. 129). 'A person was given 250 c.c. of whisky on going to bed at 10 p.m.; the urine was retained until 8 a.m. At this time, the concentration in the blood as judged from the urine was 0.11 per cent, whereas direct examination of the blood showed it to be alcohol free'.

An attractive feature of the volume is the inclusion of a short account of the various psychological tests which are commonly performed, as well as advice on the preparation of a psychiatric report for use in the courts.

A special chapter is devoted to the problems of giving psychiatric evidence, particularly in the face of severe cross-examination, when the witness may be exposed to unjust criticism or even per-

sonal abuse. Although 'an advocate must be fearless in carrying out the interests of his client, (there is) this restriction that the arms which he bears are to be the arms of the warrior and not of the assassin!'—Lord Chief Justice Cockburn, 1864.

The best protection for the medical expert is absolute honesty and a frank recognition of the limits of his knowledge. This, coupled with a deliberate determination not to be bullied into losing his temper, should protect him adequately against all comers.

Professor Macdonald's volume is to be strongly recommended to all those whose practice, in one way or another, brings them professionally into the courts.

The Problem of Suicide

Clues to Suicide. Ed. by Edwin S. Shneidman, Ph.D. and Norman L. Farberwo, Ph.D. Foreword by Karl A. Menninger, M.D. 1957. (Pp. 215 + Index. $5.50). New York: McGraw-Hill Book Company, Inc.

Contents: 1. Clues to Suicide. 2. Theories of Suicide. 3. Suicide as a Magical Act. 4. The Logic of Suicide. 5. Suicide and Age. 6. Some Aspects of the Meaning of Death. 7. The Sociology of Suicide. 8. Suicide in a Catholic Country. 9. Suicide and Law. 10. Psychotherapy of the Suicidal Patient. 11. Some Aspects of the Treatment of the Potentially Suicidal. 12. The Suicidal Crisis in Psychotherapy. 13. The Recognition and Treatment of Suicide in Children. 14. Suicide in Old Age. 15. Suicide in a General Hospital. 16. Observations on Attempted Suicide. 17. Psychologic and Social Work Clues to Suicide in a Schizophrenic Patient. 18. Suggestions for Suicide Prevention.

This volume is the work of an experienced and distinguished collection of experts drawn from Scotland, Italy and the United States of America. Dr. Karl A. Menninger has written a *Foreword* in which he sums up succinctly the scope and the purpose of this volume:

'Few people realize that suicide is more frequent than murder and more easily predicted. Early in my clinical experience I learned with astonishment how incredulous relatives and friends could be regarding the threats of patients and the warnings of doctors. To the normal person suicide seems too dreadful and senseless to be conceivable. There almost seems to be a taboo on the serious discussion of it. There has never been a wide campaign against it, as there has been against other less easily preventable forms of death. There is very little scientific research concerning it.

That is why this is an important book. It is a research study in a neglected and important area. It is the joint production of a group of scientists who have observed and collated and checked. To anyone who reviews any considerable number of suicides, it is unmistakably clear that the assigning of *the* cause or even of *the causes* for the final act is naïvely absurd and grossly misleading. But the nature and degree of the internal stress and the external evidence of it—these are a different matter. These can be found if searched for, and it is such a search that the authors have conducted through a large collection of poignant material'.

It is disturbing to realize that at least one person takes his own life every half hour round the clock in the U.S.A. Such a catastrophic feature of our society demands the earnest attention not only of professional groups but also of every citizen who harbours even the relics of a conscience.

This is a worthy and objective study which should do much to create a sounder understanding of the problem and so provide a basis of adequate preventive measures.

Medical Autobiography

A Doctor Returns. By Donald McI. Johnson. 1956. (Pp. 256. 16s.). London: Christopher Johnson Publishers Ltd.

Contents: 1. A Psychotic Episode. 2. A Conspiracy of Silence. 3. A Double Event. 4. This is the Law. 5. Humpty Dumpty. 6. A Doctor Returns. 7. Indian Hemp: A Social Menace. 8. The Mystery of Pont Saint Esprit. 9. Anticlimax. 10. Further Anticlimax. 11. The Hallucinogenic Drugs: A Neglected Aspect. 12. Scotland Yard. 13. And the Prime Minister. 14. Despotism is Unteachable. 15. I Publish My Findings. 16. Wot! No Villain? 17. The Eighth Square At Last. 18. The Problems of Mental Illness. 19. A Solution. 20. The Case of Colonel Drummond.

The author is a medical practitioner who has had an adventurous career, including the ownership of an hotel and long years of political activity culminating in his election as a Member of Parliament.

He has previously written an interesting account of *The Hallucinogenic Drugs* and is probably well known as the doctor who was detained 'involuntarily' in a mental hospital for 6 weeks, not because of 'natural illness', but because of a 'doping ruse'.

This volume is his third in a series of autobiographies written in the trenchant style which has characterized his earlier contributions.

Evidence and Proof

From Evidence to Proof: A Searching Analysis of Methods to Establish Fact. By Marshall Houts. 1956. (Pp. 379 + Index. Illustrated. 57s. 6d.). Oxford: Blackwell Scientific Publications.

Contents: 1. I Know That's the Man! 2. Eyeball Witnesses. 3. I Did It. 4. How's Your Alibi? 5. He Ran Away. 6. Sex and Its Ugly Head. 7. Insane or Psychotic. 8. I Swear It. 9. The Facts, Ma'am. 10. Emphasize your Empathy. 11. The Sheep and the Goats. 12. And it Probably Didn't. 13. Accentuate the Positive. 14. 10,000 Words. 15. For the Ear Only. 16. Figures Do Lie. 17. The Written Word. 18. The Gossamer Thread. 19. Just a Couple O'Beers. 20. Crash, Crash, Crash! 21. The Irrefutable Signature. 22. The Small Grey Line. 23. 1/100,000 of an Ounce. 24. The Hairs of Our Heads. 25. Millions of Fibers. 26. The Fragile Liquid. 27. Mother Earth. 28. Out, Damned Spot! 29. The Source of Life. 30. Murder Will Not Out. 31. Death in the Afternoon. 32. Who? 33. The Deathly Vial. Index. Appendix.

The author is a former Special Agent of the Federal Bureau of Investigation, a lawyer and a judge who has had, by virtue of his training and experience, an extensive acquaintance with the problems of fact-finding.

The emphasis of his volume is on 'how to establish the facts, to find, interpret, correlate and evaluate evidence'. He contends that most lawyers assume that admissibility implies probative value—a fallacy which is surely not as widely held as the author may believe. However, in advocating what he calls his 'adversary system', he correctly points out that 'the *objective* search for fact is possible only if the parties are equally matched. If one side fails to obtain equal representation, the other has a field day'.

Mr. Houts' volume is a lively antidote to the frame of mind which prejudges the guilt of an accused person—'the police found their suspect and then proceeded to search for the facts to fit him'. It should also prevent the development of 'prosecution complexes' and should encourage a judicial approach in the legal officer, whether acting as lawyer for the prosecution or the defence.

The volume should have a wide appeal beyond those professionally connected with the dramas of the court. It is dedicated to Erle Stanley Gardner.

The Trials of Evans and Christie

Trials of Timothy John Evans and John Reginald Halliday Christie. Edited by F. Tennyson Jesse. 1957. (Pp. 379. Illustrated. 30s.). Edinburgh: William Hodge & Co., Ltd.

On 9 March 1950, Timothy John Evans was hanged for murdering his baby daughter, Geraldine. He had, in fact (in his fourth statement to the police) also confessed to the murder of his wife Beryl, although on 3 December 1949, after having been charged with both murders, he said: 'I never done it, Mum, Christie done it'.

On 15 July 1954, John Reginald Halliday Christie was hanged for the murder of his wife Ethel. He claimed to have murdered also 5 other women since 1943 (Fuerst, Eady, Nelson, Malony, MacLennan) whose bodies or skeletons were found on the premises of 10 Rillington Place, North Kensington, where both the Evans and the Christie families had lived.

All the victims had been strangled. The unlikely coincidence of two murderers living in the same place and killing in the same way, together with the extraordinary revelations of Christie's necrophilia, led to public disquiet, a demand for an inquiry into the execution of Evans, and a debate in the House of Commons on the Scott Henderson Report on the Evans case. This report has been criticized severely for relying largely on Evans' confession and not paying enough attention to the facts in favour of Evans, although Evans was probably at least guilty of helping Christie to dispose of the body of Mrs. Evans.

The pathological evidence was given by such eminent witnesses as Dr. Donald Teare and Dr. Francis E. Camps, who has published a separate monograph on the *Medical and Scientific Investigations in the Christie Case.* The psychiatric aspects were canvassed by Dr. J. A. Hobson, Dr. D. Curran and Dr. J. C. M. Matheson.

The verbatim record of the trials is a fascinating document which forensic practitioners will read with interest and profit.